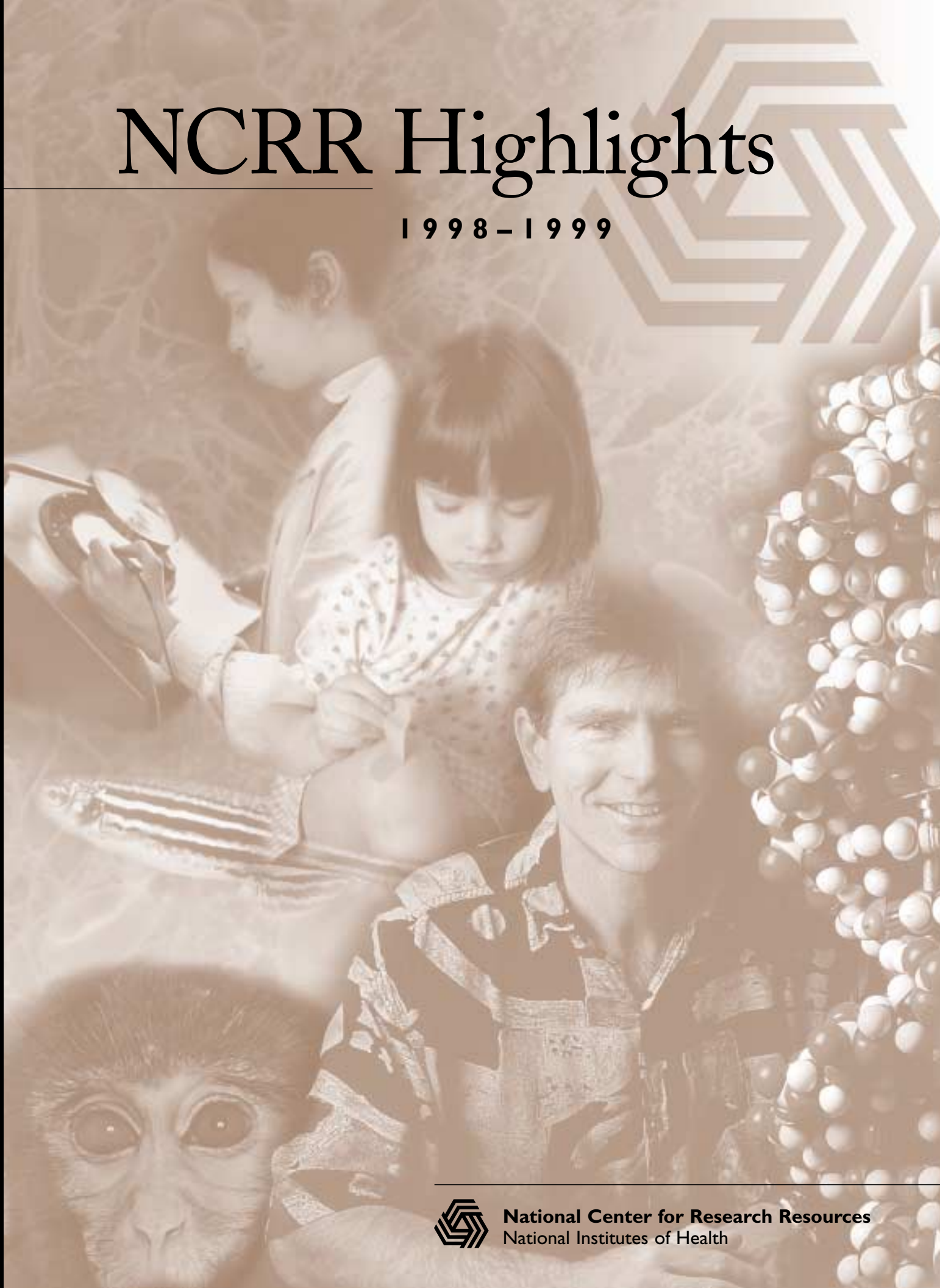
NCRR Highlights

1998–1999



National Center for Research Resources
National Institutes of Health

ON THE COVER **This collage illustrates the diverse human, animal, and technological resources that the National Center for Research Resources (NCRR) supports. Biomedical researchers who share these resources conduct basic and clinical investigations that improve human health.**

NCRR Highlights

1998–1999

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National Center for Research Resources
National Institutes of Health

MISSION

The National Center for Research Resources (NCRR) is a catalyst for discovery for NIH-supported investigations throughout the nation. NCRR creates, develops, and provides a comprehensive range of human, animal, technological, and other resources to enable biomedical research advances.

For further information about NCRR, contact:
Office of Science Policy and Public Liaison, NCRR/NIH
6705 Rockledge Drive, Room 5046
Bethesda, MD 20892-7965
Telephone: 301-435-0888
Fax: 301-480-3558
E-mail: ospio@ncrr.nih.gov
Web site: http://www.ncrr.nih.gov

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NCRR HIGHLIGHTS

Introduction

IN 1998 AND 1999, the National Institutes of Health (NIH) outlined six areas of research emphasis deemed likely to have a dramatic and positive impact on human health in the coming years. These six areas—the biology of brain disorders; genetic medicine; new approaches to pathogenesis; bioengineering, computers, and advanced instrumentation; new avenues for development of therapeutics; and new preventive strategies against disease—were judged to show great promise and likely success in addressing public health needs and so are given top priority in NIH funding decisions.

The aim of the National Center for Research Resources (NCRR) is to ensure that scientists in these and many other biomedical fields have access to the research tools and infrastructure they need to conduct cutting-edge science. As such, NCRR's mission is unique among the 25 institutes and centers that make up NIH. While the other NIH institutes and centers focus on particular diseases, organ systems, or categories of research, NCRR alone has a trans-NIH mandate: to support the research infrastructure that enables all lines of biomedical inquiry, ranging from studies of molecules to humans. Simply put, NCRR gives biomedical scientists the tools they need to advance understanding of human health.

This publication, *NCRR Highlights 1998–1999*, illustrates how NCRR-supported research resources enable critical advances in each of the six NIH priority areas. The publication also defines NCRR's four scientific areas—Clinical Research, Biomedical Technology, Comparative Medicine, and Research Infrastructure—and the research resources they support. By providing scientists nationwide with access to advanced technologies, research facilities, laboratory animals, and biological materials, NCRR serves as a facilitator—or catalyst—for biomedical discovery.

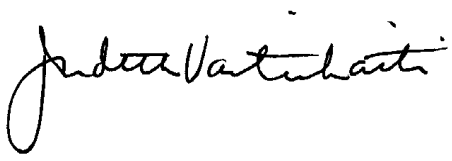
Staying abreast of needed tools and technologies in the fast-moving fields of biomedical science is a formidable task. Unanticipated

discoveries often create unpredictable demands for new infrastructure. For instance, many of today's most rapid and widely used tools for gene and protein analysis were unheard of just over five years ago, yet today these instruments provide critical insights into countless genetic disorders and conditions. NCRR helps to ensure that scientists have access to essential technologies.

Meeting and anticipating emerging infrastructure needs requires NCRR to maintain an ongoing dialogue with the biomedical research community. One way this is accomplished is through NCRR's strategic planning process, which lays a framework for setting priorities and making judicious use of public funds. NCRR's most recent planning document, *NCRR: A Catalyst for Discovery—A Plan for the National Center for Research Resources 1998–2003*, was developed in partnership with hundreds of biomedical investigators from across the country. Published in 1998, this comprehensive plan identifies more than 50 opportunities by which NCRR might enhance the nation's biomedical research infrastructure over a five-year period. As 1999 drew to a close, NCRR had already acted on many of the proposed opportunities.

To stay flexible and responsive to ever-changing scientific demands, NCRR regularly interacts with biomedical investigators through workshops, expert panel meetings, and other means to track emerging research trends. For instance, when advances in stem cell technologies offered new opportunities for studying and preserving these versatile cells, NCRR responded to workshop recommendations by requesting applications for a grant to establish a new national stem cell resource, which will maintain and distribute nonhuman-derived stem cells to the biomedical research community. When two expert panels noted an alarming reduction in the number of investigators entering clinical research, NCRR responded by modifying and expanding its career development programs for clinical researchers. And when a working group of the White House Office of Science and Technology Policy recognized a critical need for bioinformatics resources in all areas of biomedical science, NCRR's Clinical Research area launched an annual meeting on bioinformatics and its application to clinical research.

It is NCRR's belief that ready access to essential research resources positions scientists to seize emerging opportunities and expand the understanding of biological processes. In this way, NCRR is critical to the NIH mission: To improve the treatment and prevention of human disease and to enhance the health of our nation's citizens.



JUDITH L. VAITUKAITIS, M.D.
Director, National Center for Research Resources

What Are Research Resources?

CUTTING-EDGE TOOLS have always played a critical role in medical discovery. From the early microscopes that enabled the first observations of cells in the 16th century to the DNA sequencers that today analyze the genomes of dozens of organisms, research tools permit scientists to probe aspects of biology that may be otherwise undetectable.

Today, as we enter a new millennium, the requisite tools for conducting cutting-edge biomedical science are extraordinarily sophisticated—and expensive—yet they offer unprecedented opportunities for exploring and enhancing human health. Providing such essential tools to biomedical scientists is NCRR's mission. By NCRR's definition, research resources include not only advanced technologies and instruments but also clinical research environments, animal models, new and renovated buildings and laboratories, and a cadre of well-trained scientists and research support staff. These critical research resources lay a solid foundation for new discoveries in health-related science. Each year NCRR-funded research resources support the research endeavors of more than 20,000 investigators who have approximately $2.3 billion in primary research grants provided by the categorical institutes of NIH.

One of NCRR's primary goals is to maximize the use of scarce or expensive resources by providing them on a shared basis to many investigators, thereby increasing efficiency and stretching federal research dollars. Shared resources also provide a fertile environment for interdisciplinary studies and the sharing of expertise, which is especially important to rapidly evolving fields such as functional genomics and structural biology. NCRR places particular emphasis on providing research

resources that are:

- cost-saving, efficient, shared, and accessible;
- multidisciplinary and collaborative, often serving to integrate diverse research efforts; and
- at the cutting edge of innovation, including high-risk and long-term research that may have significant societal payoff.

NCRR research support is concentrated in four areas—Biomedical Technology, Clinical Research, Comparative Medicine, and Research Infrastructure. Together these areas ensure that the biomedical community has access to cross-cutting research resources that serve all branches of scientific inquiry supported by NIH.

NCRR's Biomedical Technology area funds resource centers that enable development of advanced instruments, technologies, and techniques, including mass spectrometers, computational tools, and imaging devices. Qualified scientists from outside these centers may seek expert advice of the core resource staff, gain access to unique technologies, or attend training sessions at these state-of-the-art resource centers. The Biomedical Technology area also awards Shared Instrumentation Grants, which provide funds to institutions for the purchase of expensive instruments that, although prohibitively expensive to an individual investigator, can be cost-effective when shared among several researchers.

NCRR's Clinical Research area supports a nationwide network of approximately 75 General Clinical Research Centers (GCRCs), which are self-sustained research environments for the study of human subjects. Usually located within major academic medical centers or teaching hospitals, each GCRC contains beds, laboratory facilities for specialized tests, computer facilities, and a dedicated staff of research nurses and other support personnel. Some GCRCs also include specialized facilities such as diet kitchens and metabolic study units. Qualified investigators whose research is supported by NIH may use the controlled environment of the GCRC to conduct cost-effective studies on humans; elsewhere such facilities might be prohibitively expensive or technically difficult to access and use. Among the numerous GCRC-supported studies now under way are investigations of obesity, diabetes, cancer, AIDS, and stroke.

Animal models of human health and disease are integral components of the research enterprise and provide a vital link between basic research and clinical studies. Nonhuman primates, in particular, are so closely related to humans that studies of these animals offer crucial insights into the pathobiology and treatment of devastating conditions such as AIDS, cardiovascular disorders, and drug addiction. NCRR's Comparative Medicine area supports eight Regional Primate Research Centers, which supply nonhuman primates to qualified investigators and provide collaborative opportunities for them to work at the centers. Other Comparative Medicine resources provide scientists with well-characterized laboratory animals ranging from mice and fish to flies and roundworms.

To provide opportunities for members of minority groups to participate in frontline research, NCRR's Research Infrastructure area supports the establishment and operation of approximately 18 Research Centers in Minority Institutions (RCMI). In these centers, which are associated with predominately minority universities that offer doctorate degrees in health-related sciences, researchers have access to advanced instrumentation, modern facilities, and other research support. Because many investigators at RCMI institutions study diseases that disproportionately affect minorities, NCRR support serves the dual purpose of bringing more minority scientists into mainstream research and enhancing studies of minority health. The Research Infrastructure area also awards extramural construction grants that match institutional funding to support new and ongoing construction projects at research facilities nationwide.

The multifaceted research resources and resource-related projects supported by NCRR's four areas cover the spectrum of biomedical research. By virtue of its trans-NIH nature, NCRR is uniquely positioned to help scientists transcend barriers to interdisciplinary research and move discoveries from bench to bedside.

Research Areas

NCRR HIGHLIGHTS 1998–1999

THE NCRR CLINICAL RESEARCH (CR) area provides resources that enable clinical investigators to rapidly and effectively respond to research needs stemming from current and emerging health issues.

A national network of approximately 75 General Clinical Research Centers (GCRCs), located at U.S. academic medical centers, offers investigators specialized environments to study prevention and treatment of many diseases that affect adults and children, such as heart disease, cancer, diabetes, and AIDS. Each year, GCRCs host about 8,200 investigators who conduct more than 6,100 clinical research projects.

Through the Clinical Associate Physician award, the CR area supports career development of clinical investigators who have made a commitment to focus their research endeavors on patient-oriented research.

To expedite gene therapy research, NCRR and other NIH components cofund three National Gene Vector Laboratories to produce and distribute sufficient quantities of high-quality clinical-grade vectors for use in patient therapies.

The CR area also supports the National Disease Research Interchange, a resource that collects and distributes samples of human tissues and organs, both normal and diseased.

Accomplishments

- Collaborated with the Cystic Fibrosis Foundation to fund an interactive network of Therapeutic Development Centers at institutions that have NCRR-supported General Clinical Research Center (GCRC) Coordinating Centers and a GCRC bioinformatics core. The collaboration will accelerate the development of new therapies by evaluating new drugs and biological agents in multicenter trials linked by clinical coordinating centers.

- Expanded the Clinical Associate Physician (CAP) program to assure a well-trained cadre of physician investigators. The CAP program helps provide a bridge between basic and patient-oriented research.

- Utilized the Midcareer Investigator Award in Patient-Oriented Research by offering clinicians protected time to devote to patient-oriented research and to act as mentors for novice clinical investigators. Targeted candidates are outstanding clinical scientists who are actively engaged in patient-oriented research.

- Funded a Neurobehavioral Research Unit for the GCRC at Johns Hopkins University in Baltimore, Maryland. The facilities of this unit will enable investigators to add neurophysiology and neuroimaging capabilities, including functional magnetic resonance imaging (fMRI), MR spectroscopy, and MRI-compatible electroencephalogram monitoring.

Clinical Research

- Funded a Pharmacogenetics Core Laboratory at the GCRC at the University of Pittsburgh. This centralized laboratory provides cutting-edge pharmacogenetic technology and expertise in the area of clinical outcomes analysis and pharmacogenetic endpoint measurement using state-of-the-art molecular biological approaches.

- Funded a new Clinical Genetics Research and Consultation Center at the University of Utah GCRC in Salt Lake City. The Center will focus on dysmorphology, the measurement of anthropometric parameters in children with hereditary disorders.

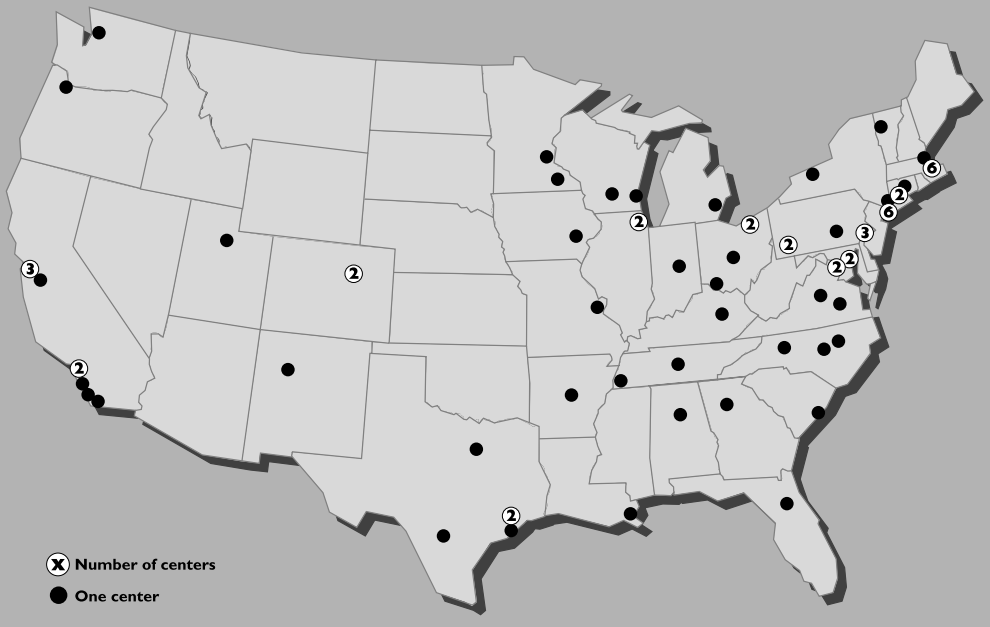
- Expanded the National Gene Vector Laboratories Program to accept applications from investigators for adeno-associated virus, herpes simplex virus, and lentivirus; to accept requests for support of vector preclinical toxicology studies; and to support development of a generally accessible "master file" for toxicology in order to facilitate "investigative new drug" applications to the Food and Drug Administration.

- Supported annual meetings of the GCRC program directors and staff.

- Established new GCRCs at the State University of New York in Stony Brook, the University of Arkansas for Medical Sciences in Little Rock, and Georgetown University in Washington, DC.

- Established University of Pittsburgh GCRC satellite units at Magee Women's Hospital and the Western Psychiatric Institute and Clinic, and a University of Southern California (Los Angeles) GCRC satellite unit at the City of Hope National Medical Center in Duarte.

GENERAL CLINICAL RESEARCH CENTERS



THE NCRR BIOMEDICAL TECHNOLOGY (BT) area makes the newest and most advanced technologies, techniques, and instruments available to the biomedical research community. Scientists at approximately 60 Biomedical Technology Resource Centers nationwide lead research teams to discover, create, and develop technological innovations that have applications to a broad spectrum of biomedical research activities. Subsequently, these technologies and methodologies are disseminated to the biomedical research community. These resource centers emphasize bioengineering, flow cytometry, integrated technologies, isotopes and particles, laser applications, magnetic resonance imaging, magnetic resonance spectroscopy, mass spectrometry, optical and electron microscopy, simulation and computation, and synchrotron radiation.

The BT area also supports investigator-initiated research projects, including those that are innovative, developmental, and exploratory, to create new or improved instruments and technologies that support biomedical research technology needs. These research projects may lead to future resources.

The Shared Instrumentation Grant Program enables institutions with a high concentration of NIH-supported researchers to purchase commercially available instruments that cost more than $100,000 for shared use by a number of researchers.

Small Business grants support both innovative research projects for new or improved biomedical technologies of scientific merit and collaborative technology transfer activities to facilitate commercial development.

Accomplishments

- Supported development of innovative software, algorithms, and techniques for use with high-performance computers and telecommunication facilities. This development will increase the number of biomedical technology resources and applications that can be remotely accessed by investigators over the next generation of the Internet, which will be 1,000 times faster than the current Internet.

- Funded 10 new Biomedical Technology Resource Centers, bringing the total number of NCRR-supported centers hosted by institutions across the country to 67 at the close of 1999. The new centers provide unique capabilities in the areas of bioengineering, integrated technologies, magnetic resonance imaging, mass spectrometry, simulation and computation, and synchrotron radiation.

- Cofunded (with the National Institute of General Medical Sciences) an NIH and Department of Energy (DOE) initiative to upgrade two of the nation's premier synchrotron X-ray facilities: The Stanford Synchrotron Radiation Laboratory at a DOE resource at Stanford University in California and the National Synchrotron Light Source at the DOE Brookhaven National Laboratory in New York. These technological upgrades will dramatically improve capabilities to determine the structures of important molecules and will help meet researchers' exponentially growing demands for access to these research facilities.

Biomedical Technology

- Utilized the Shared Instrumentation Grant (SIG) Program to support 92 awards in 1998 for the purchase of cutting-edge instruments. In 1999, with a large increase in the SIG appropriated budget, 139 grants were awarded. Instruments purchased with SIGs must cost more than $100,000 each. Today, these high-sensitivity and high-resolution instruments, used on a shared basis among a number of investigators, are at the forefront of biomedical research.

- Increased the ceiling of the Shared Instrumentation Grant awards from $400,000 to $500,000 beginning with grant applications selected for funding in 2000.

- Supported research to discover innovative approaches to developing technologies that would explore new research paradigms in engineering, instrumentation, physical sciences, mathematics, and computer science.

- Participated in several trans-NIH funding initiatives to support basic bioengineering research and bioengineering research partnerships that would be likely to advance health or health-related research. Such partnerships must include bioengineering expertise combined with basic or clinical investigations.

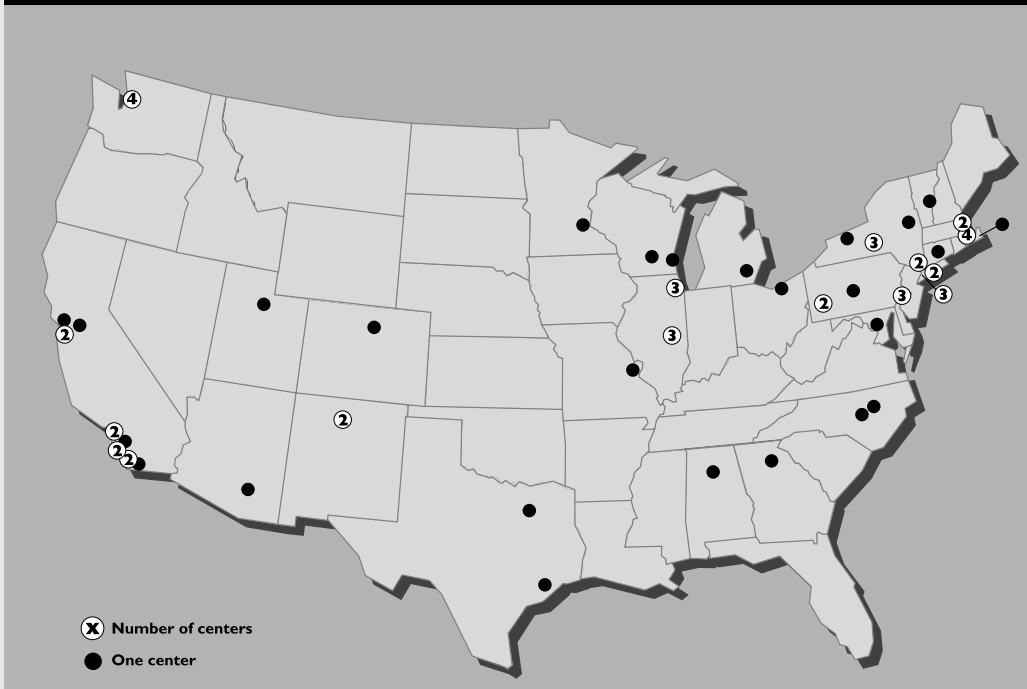
- Sponsored the "Integrated Genomics Technologies Workshop" with assistance of several NIH institutes, the Department of Energy, the National Science Foundation, and the Los Alamos National Laboratory. The workshop focused on identifying the biological challenges of the future and the technological responses required to fully characterize the genomics and proteomics of the intact living cell.

- Sponsored "In-Vivo Microscopy: Technologies and Applications" workshop. Although an extraordinary body of research in imaging technologies and applications has been developed over the last 25 years, the majority of the work has focused on clinical application of these technologies. This workshop explored the state-of-the-art in small animal imaging research, identified the major challenges facing the field, identified the most immediate applications of small animal imaging, and defined specific directions for federal support.

- Participated in activities of the Research Resources and Infrastructure Working Group Subcommittee on Biotechnology, National Science and Technology Council, White House Office of Science and Technology Policy, and supported a workshop on bioinformatics. Experts in bioinformatics and related fields attended to assess the current state of bioinformatics and to recommend future roles for the federal government and other entities.

- Supported the workshop on "Opportunities in Molecular Biomedicine in the Era of Teraflop Computing." Experts in this field explored the potential benefits of and need for teraflop resources in biomedical science. Such capabilities will permit more detailed understanding of the molecular basis of disease, drug actions, and functional genomics.

BIOMEDICAL TECHNOLOGY RESOURCE CENTERS



THE COMPARATIVE MEDICINE (CM) area supports research activities that explore, develop, and maintain a variety of high-quality research animals and other biological models needed by the biomedical research community for studies of human health and disease.

Eight Regional Primate Research Centers (RPRCs) maintain nonhuman primates as models of human disorders and diseases for biomedical and behavioral research. The RPRCs provide a special environment for more than 18,000 nonhuman primates, mostly macaques. These animals have broad applications to biology, medicine, behavior, and health. The RPRCs are academic environments of high standards for as many as 1,400 investigators, including staff and visiting scientists, who conduct research there.

The national NIH Chimpanzee Management Program supports long-term, cost-effective housing and maintenance at chimpanzee biomedical research facilities for chimpanzees that are owned by NIH for biomedical research.

New and improved animal models help to advance studies of normal cell functions and pathological conditions. Repositories supported by the CM area offer investigators genetic stocks such as transgenic and "knockout" mice, *C. elegans*, and zebrafish. The CM area also provides training and career development opportunities.

In addition, the CM area fosters the development of important animal-related resources that broaden the utility of animal models. These resources are diverse and include animals of defined genetic backgrounds, DNA arrays for analysis of gene expression, and computer models.

Accomplishments

- Established a new Regional Primate Research Center (RPRC) at the Southwest Foundation for Biomedical Research in San Antonio, Texas. The Southwest RPRC joins a network of NCRR-supported RPRCs that may be accessed by the biomedical research community to conduct investigations that require nonhuman primate models of human diseases.

- Established the Microarray Resource for *C. elegans* at Stanford University in California to make expensive and difficult microarray technology available to a broad group of investigators. Results of gene expression studies with this technology will be instrumental in determining the function of human genes, which are often similar to those of *C. elegans.*

- Supported the National Zebrafish Resource, a repository for strains of this important model, at the University of Oregon in Eugene. The resource developed a widely used database, Z-FIN, which is instrumental in communicating general and genome-related information on zebrafish.

- Funded the Yeast Genetic Stock Center at the American Type Culture Collection in Manassas, Virginia, to acquire, authenticate, preserve, produce, develop, and distribute genetically defined strains of the yeast *Saccharomyces cerevisiae* and related biological materials and information.

Comparative Medicine

- Established a Baboon Research Resource at the University of Oklahoma Health Sciences Center, Oklahoma City, to support studies on captive baboons and provide a resource of laboratory-born and laboratory-reared animals for NIH-sponsored research.

- Initiated efforts to establish molecular typing laboratories at the Wisconsin Regional Primate Research Center, Madison, to screen for major histocompatibility complexes of immune cells, which are important for combating infectious diseases.

- Established the NIH Chimpanzee Management Program (ChiMP) within NCRR to address the appropriate housing, maintenance, and use of chimpanzees in biomedical research.

- Sponsored international workshops on embryonic stem cells and on the cryopreservation of animal gametes and embryos. Cryopreservation of animal gametes and reproductive cells and tissues will play an increasingly important role in investigations of the molecular basis of human diseases.

- Funded two Mutant Mouse Regional Resources (MMRRs) at the University of California, Davis, and the University of North Carolina, Chapel Hill. These resources enhance the availability and quality of genetically altered mice. Each MMRR is capable of maintaining and providing animals; cryopreserving, storing, and reconstituting embryos; and supporting these activities with administrative and quality-control infrastructure.

REGIONAL PRIMATE RESEARCH CENTERS

THE NCRR RESEARCH INFRASTRUCTURE (RI) area supports diverse programs and projects that develop, expand, and invigorate the nation's biomedical research infrastructure.

The Research Centers in Minority Institutions (RCMI) Program increases the capacities of minority colleges and universities that offer doctorates in health sciences to conduct biomedical and behavioral research. Similarly, the RCMI Clinical Research Infrastructure Initiative (RCRII) assists RCMI institutions affiliated with medical schools to develop and expand their capacities to conduct clinical research.

The Research Infrastructure at Minority Institutions (RIMI) project enables minority institutions that offer bachelor's or master's degrees in health-related science to develop and build their biomedical research capabilities through collaborations with nearby, research-intensive institutions that offer doctoral degrees.

The Research Facilities Improvement Program provides institutional grants to improve or construct facilities and upgrade animal facilities at institutions that support Public Health Service-sponsored research.

The Science Education Partnership Award (SEPA) encourages scientists to work with educators and community organizers to increase student and public understanding of science.

The Institutional Development Award (IDeA), which broadens the geographic distribution of NIH grant funding, develops biomedical researchers' competitiveness at institutions in states that are eligible for this award.

Accomplishments

- Supported construction of the nation's first full-scale biosafety level-4 (BL4) laboratory at a non-government institution. Located at the Southwest Foundation for Biomedical Research in San Antonio, Texas, the new facility will enable study of emerging, highly dangerous pathogens.

- Established new Research Centers in Minority Institutions (RCMI) at Jackson State University in Mississippi and at the University of Texas at San Antonio. Jackson State used RCMI funding to create a Center for Environmental Health, and the University of Texas established a Neuroscience Research Center, which promotes interactions between neuroscientists and computer scientists.

- Sponsored the Sixth International AIDS Symposium. This four-day meeting was attended by more than 500 scientists. Participants described recent research findings and collaborations, including a report on how genetic mutations affect HIV susceptibility in various ethnic populations.

- Collaborated with the National Institute of Neurological Disorders and Stroke and the NIH Office of Research on Minority Health to fund five Specialized Neuroscience Research Programs at Minority Institutions. The Centers are located at the University of Hawaii at Manoa, Howard University in Washington, DC, the University of Texas in San Antonio, the University of Puerto Rico Health Sciences Center in San Juan, and the Universidad Central del Caribe in Puerto Rico.

Research Infrastructure

- Established Centers of Clinical Research Excellence at the University of Hawaii at Manoa, Charles R. Drew University of Medicine and Science in Los Angeles, and the Morehouse School of Medicine in Atlanta, Georgia. The long-range goal of this funding initiative is to expand clinical research capacities at minority institutions by the recruitment and retention of competitive clinical investigators.

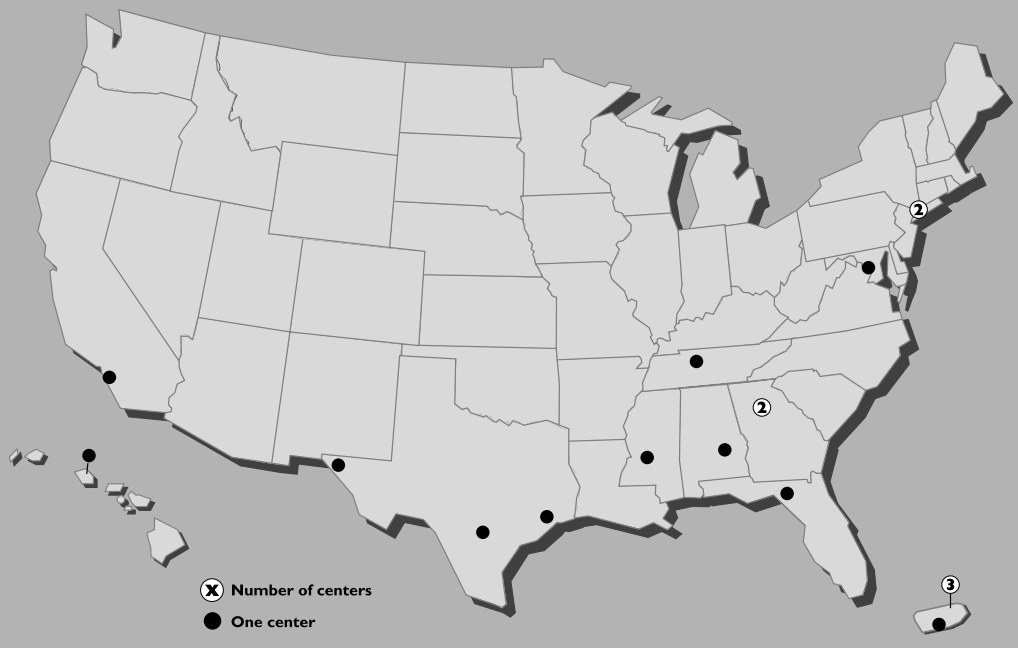
- Provided continuing support to CityLab, a regional biotechnology learning laboratory for teachers and students at Boston University School of Medicine. With funding from a Science Education Partnership Award (SEPA), CityLab has developed satellites and mobile labs (Shuttle Labs) throughout New England to introduce high school and middle school students and their teachers to state-of-the-art biomedical technologies. More than 8,500 students (one-third of whom are minorities) have used CityLab, and 800 teachers have been certified.

- Enabled a team of scientists and educators at Baylor College of Medicine to work with school districts, teachers, and parents to identify significant gaps in health and science educational materials related to national curriculum and health priorities. With SEPA funding, the team proposed creation of a new interdisciplinary K–12 model that will integrate science, health, reading, and math. Materials known as big books and student story books, as well as inquiry-based and take-home activities for students and their families, will be developed, tested, and disseminated. More than 1,000 teachers and nearly 25,000 students and their families will benefit from the proposed activities.

- Awarded grants through the Research Facilities Improvement Program to support 56 new construction projects in 1998 and 1999 at biomedical research institutions nationwide. These competitively awarded grants help provide sophisticated research facilities that spawn new research activities and improve research effectiveness and capacity.

- Utilizing the Animal Facilities Improvement Program, funded 30 facility alteration and renovation projects, including doubling the number of biosafety levels 2 and 3 facilities at eight NCRR-supported Regional Primate Research Centers.

RESEARCH CENTERS IN MINORITY INSTITUTIONS



Research Highlights

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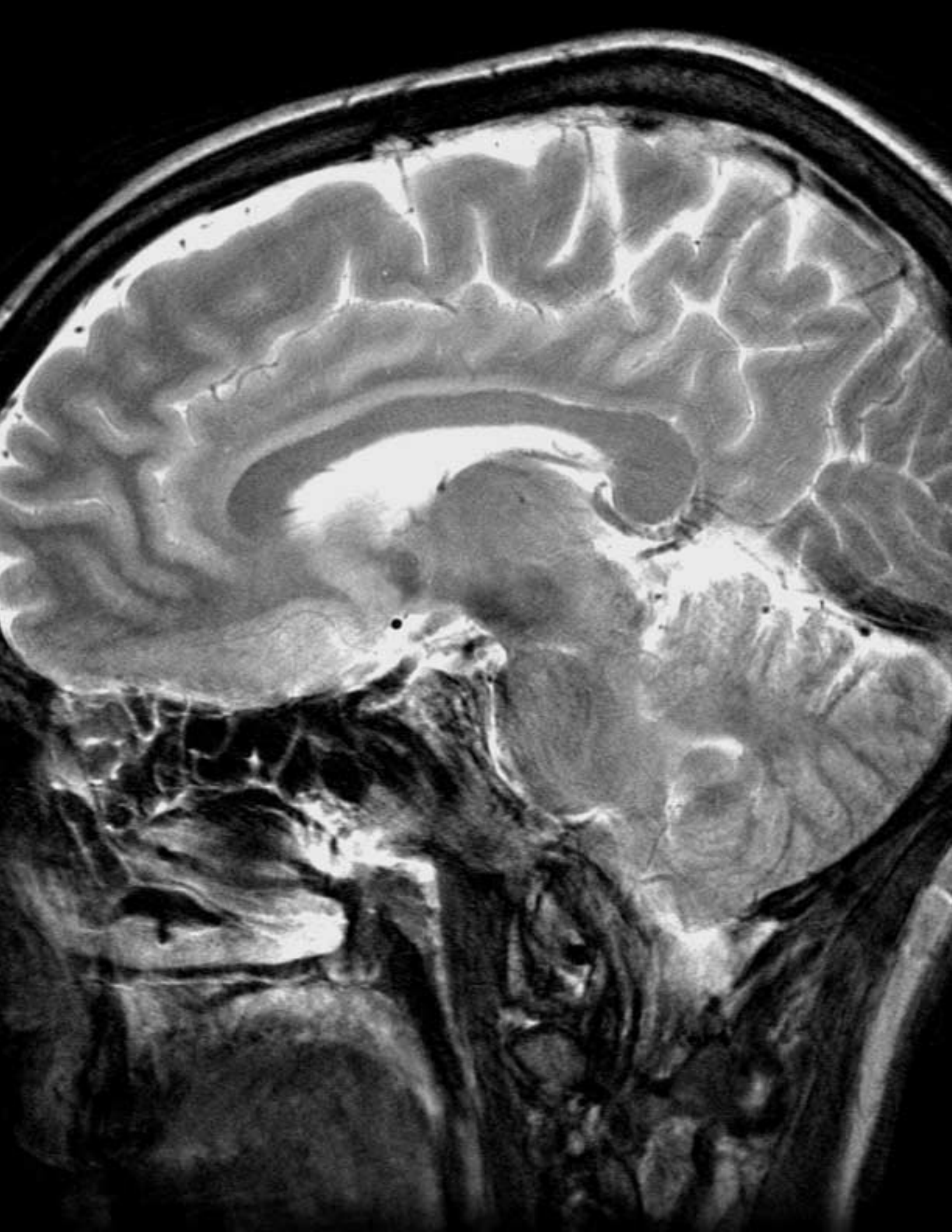


Biology of Brain Disorders

BRAIN RESEARCH, like research in other areas of the body, must delve into relatively straightforward issues, such as identifying the structure, location, and function of nerves and the production and function of enzymes and hormones. But unlike investigators in other disciplines, brain researchers also face esoteric and less tangible questions that relate to thought processes and memory, decision making, and emotions.

Scientists at the NCRR-supported Center for Advanced Magnetic Resonance Technology can acquire high-resolution images of the human brain in action. *Image courtesy of Dr. Gary H. Glover, Stanford University School of Medicine*

As the selected abstracts of research accomplishments show, NCRR support touches both tangible and less tangible areas. The support includes instrumentation and research animals that allow investigators to study brain functions and disorders that include memory, Alzheimer's disease, hormone processing, and prion diseases.

As the "Decade of the Brain" draws to a close, investigators can rightfully claim major research accomplishments. But as is often the case, new discoveries pose new questions. In the years to come, the brain will still contain the largest number of functions without known mechanisms within the human body.

Lighting the Corners of the Mind. Experiences are remembered or forgotten, but how and where they are stored or lost is largely an unknown area in brain research. Using functional magnetic resonance imaging (fMRI), scientists at the NCRR-supported Center for Advanced Magnetic Resonance Technology at Stanford University identified specific brain activations that differentiated between visual or verbal experiences that were later remembered well, remembered less well, or forgotten. Study participants underwent brain scans as they viewed photographs or were asked to memorize visually presented words. Later participants were tested for how well they remembered each item.

Dr. Marie Filbin and her colleagues report that nerve growth factors known as neurotrophins show promise for restoring damaged neurons. *Photo courtesy of Hunter College of the City University of New York*

The experiments showed that the degree of activation of the right frontal and bilateral parahippocampal regions of the brain predicted how well a particular visual experience would be recalled, and sustained activation in a related brain region predicted how well words were recollected.

These findings show that the technique of fMRI is now so advanced that it is possible to study details of memory retention and loss, a topic of great relevance to the increasing number of aging Americans.

—*Hippocampus* 9:35-44, 1999; *Science* 281:1185-1187, 1998.

Nerve Regrowth: New Hope for Injured Patients. A classical dogma in biology states that the central nervous system, which includes the brain and spinal cord, cannot regenerate after damage. But recent evidence suggests that under appropriate conditions neurons will regrow axons, offering hope that in the distant future a treatment might be developed for certain types of paralysis.

Supported by NCRR's Research Infrastructure area, scientists at Hunter College of the City University of New York had previously shown that a component of the myelin membrane, which surrounds and insulates nerves, inhibits regrowth of damaged neurons. In their new studies, the investigators discovered that bathing the neurons in nerve growth factors known as neurotrophins can prevent growth inhibition by the myelin component called myelin-associated glycoprotein, or MAG. The scientists suggest that incubation with neurotrophins elevates the concentration of the powerful regulating substance

cyclic AMP, which activates an enzyme that blocks MAG inhibition of nerve regrowth.

The researchers are now adapting these in vitro findings to in vivo conditions and working to determine the optimal neurotrophin concentrations for different types of neurons.

—*Neuron* 22:89-101, 1999.

Early Diagnosis of Parkinson's Disease. A serendipitous discovery more than a decade ago has led to an imaging technique for early diagnosis of Parkinson's disease. Scientists at the NCRR-supported New England Regional Primate Research Center in Southborough, Massachusetts, discovered that tropane—a chemical that is structurally similar to cocaine—bound specifically to substances in the brain known as dopamine transporters. These transporters carry the neurotransmitter dopamine back to the nerve cells that produced it after it has exerted its effect on target nerve cells. Destruction of these dopamine-producing nerve cells is a principal cause of Parkinson's disease, which affects about 1 million Americans.

The investigators found that a radioactively labeled derivative of tropane, known as altropane, also selectively binds to the dopamine transporters and can be detected by single-photon emission computed tomography. Preliminary studies of monkeys with a Parkinson-like condition confirmed that altropane imaging could identify animals with insufficient dopamine-producing cells in the brain. Follow-up clinical evaluations of both healthy volunteers and patients with Parkinson's disease further demonstrated the new imaging agent is a sensitive and effective marker for Parkinson's disease.

This novel imaging procedure may enable earlier diagnosis of Parkinson's disease than current methods. Because 60 percent to 80 percent of the dopamine-producing nerve cells may be lost before symptoms appear, early diagnosis will greatly enhance the effectiveness of treatments to preserve remaining neurons.

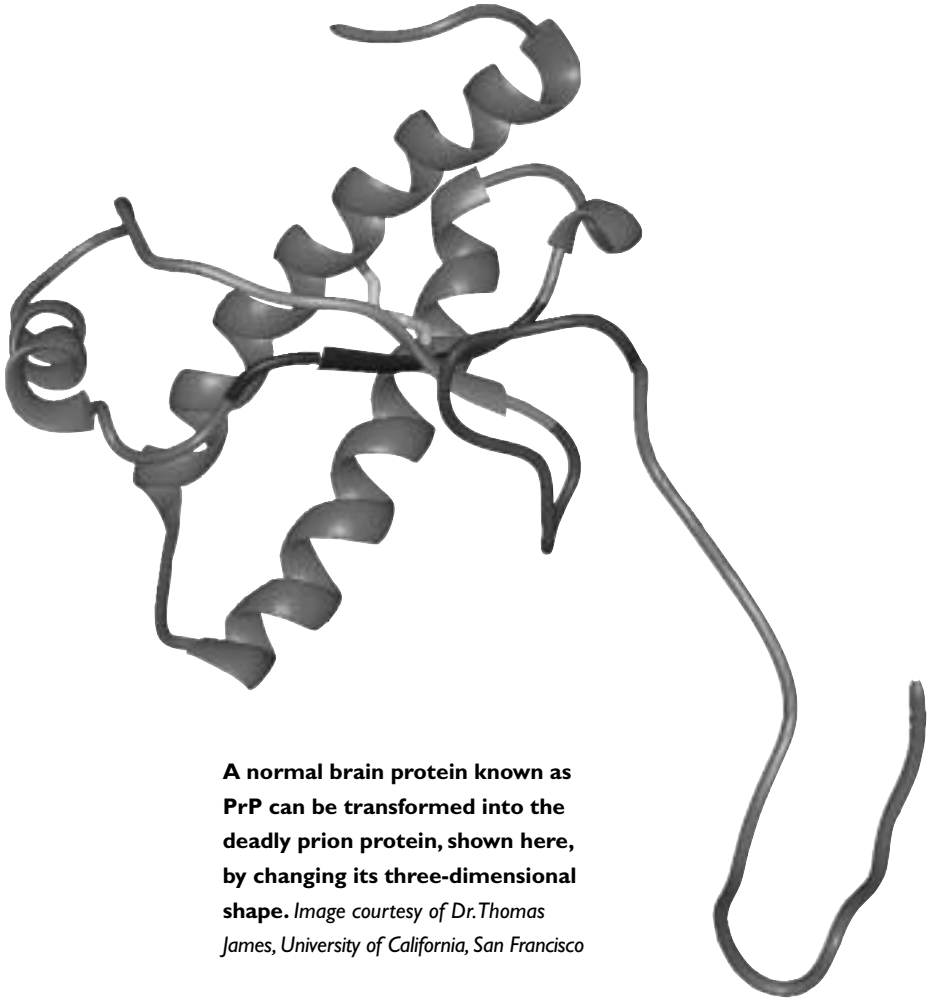
—*Synapse* 29:93-141, 1998.

Tracking Hormone Processing in Single Aplysia Neurons. What the bacterium *Escherichia coli* is to geneticists, the shell-less cold-water snail *Aplysia* is to neurobiologists. The snail, also known as sea hare because its long antennae resemble rabbit ears, is an essential organism for the study of developmental biology, the nervous system, and the

Dr. Bertha Madras and her colleagues are developing a quick and simple imaging agent for the study and diagnosis of Parkinson's disease. *Photo courtesy of Harvard Medical School*

physiological basis of learning and memory. The NCRR-supported NIH-National Resource for Aplysia, located on Virginia Key in Florida, is the only facility in the world that breeds these animals and provides them to scientists worldwide.

Studying animals provided by the NIH resource, researchers at the University of Illinois at Urbana-Champaign have adopted a mass spectrometric procedure that allows them to identify and quantitate minute amounts of peptide hormones in single neurons. The procedure, known as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), is a technique that introduces a sample into the gas phase for MS analysis. In contrast to conventional analytical methods that require cells to be disrupted before analysis, MALDI-TOF MS can measure the contents of single cells without prior disruption.



A normal brain protein known as PrP can be transformed into the deadly prion protein, shown here, by changing its three-dimensional shape. *Image courtesy of Dr. Thomas James, University of California, San Francisco*

Using this sensitive method, the Illinois investigators elucidated in detail how a 271-amino acid precursor to the egg-laying hormone and several other *Aplysia* peptide hormones is processed, and how the resulting active hormones are distributed to their respective targets. In addition to showing that earlier schemes of the processing of these hormones were incomplete, the scientists demonstrated that individual animals may show slight variations in their complement of peptide hormones. Subtle variations of this type would have been lost in traditional techniques that employ a pool of disrupted cells from many animals.

—*Proceedings of the National Academy of Sciences USA* 95:3972-3977, 1998.

Nuclear Magnetic Resonance Provides Clues to Prion Puzzle. Proteinaceous infectious particles, or prions, have the same basic composition as a normal brain protein known as PrP, but the three-dimensional (3-D) shape, or conformation, of the two molecules is dramatically different. Prions have been generally recognized as the cause of a group of deadly brain diseases known as spongioform ence-

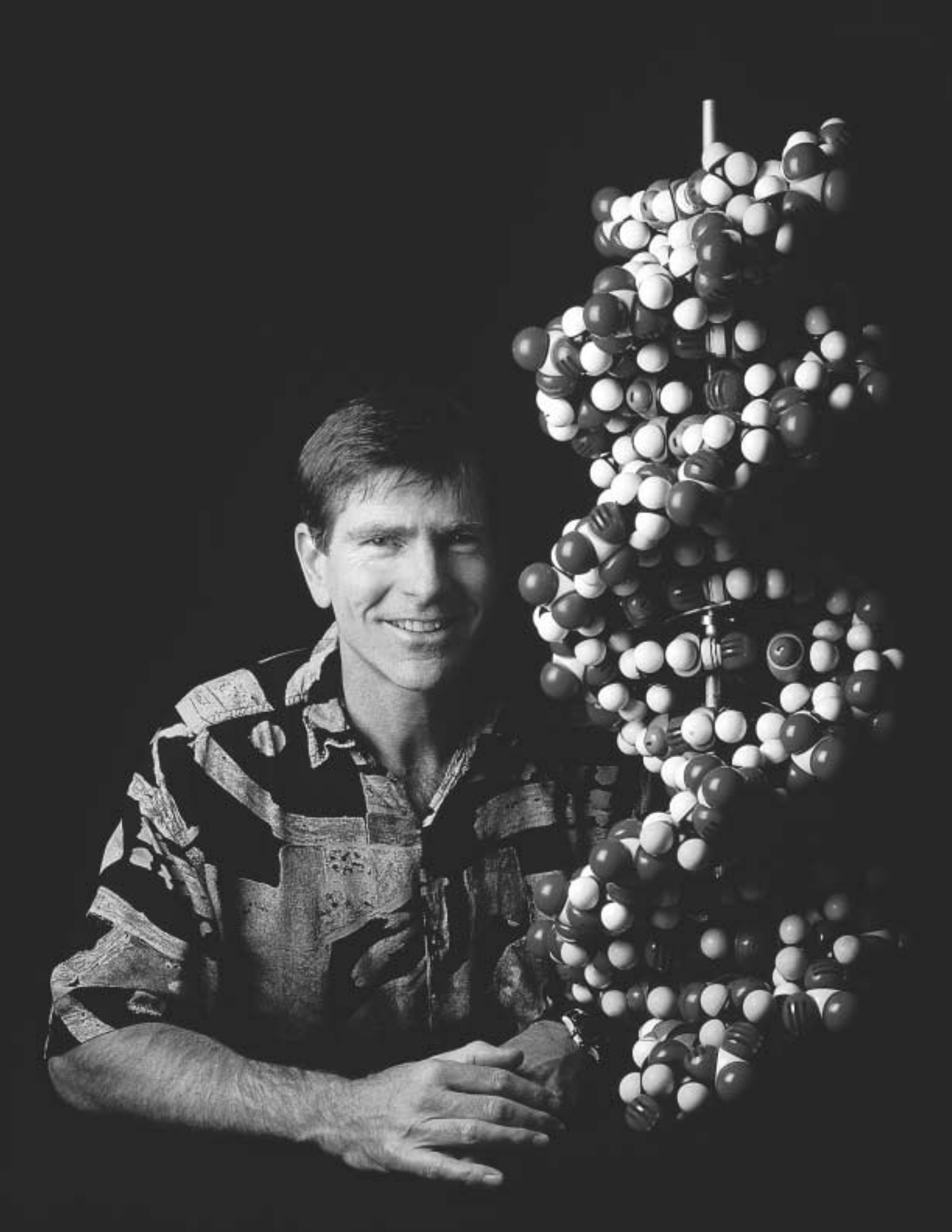
phalopathies, which affect both animals and humans and can be either inherited or acquired. It has been unclear, however, what causes the intrinsic, benign PrP to change its 3-D shape and become pathogenic.

Using state-of-the-art instruments—purchased through the NCRR Shared Instrumentation Grant Program—as well as an NCRR-supported biomolecular graphics resource at the University of California, San Francisco, scientists have determined the 3-D structure of a prion protein. The protein consists of three alphahelical, or screw-shaped, sections and two flattened sections known as beta-sheets. Using nuclear magnetic resonance spectroscopy, the researchers observed that when the protein folds into its regular conformation, a particular amino acid is positioned at a critical juncture that participates in several different conformations. In an earlier study the investigators showed that this part of the prion protein folds into the shape of the normal protein in some solutions, but under other conditions it may take the shape associated with the infectious particle.

By identifying particular amino acids at the critical junction, the most recent study explains how a genetic mutation might lead to a rare inherited form of prion disease, such as fatal familial insomnia. Substitution of only one or two amino acids at this critical location can disrupt stabilizing hydrogen bonds and thereby change the protein's conformation.

Because it is known that animals with certain types of amino acids at particular locations in the protein do not get prion diseases, the scientists suggest that farm animals could be made resistant to "mad cow" disease and other prion diseases by genetic engineering and subsequent breeding of selected animals.

—*Biochemistry* 38:5362-5377, 1999.



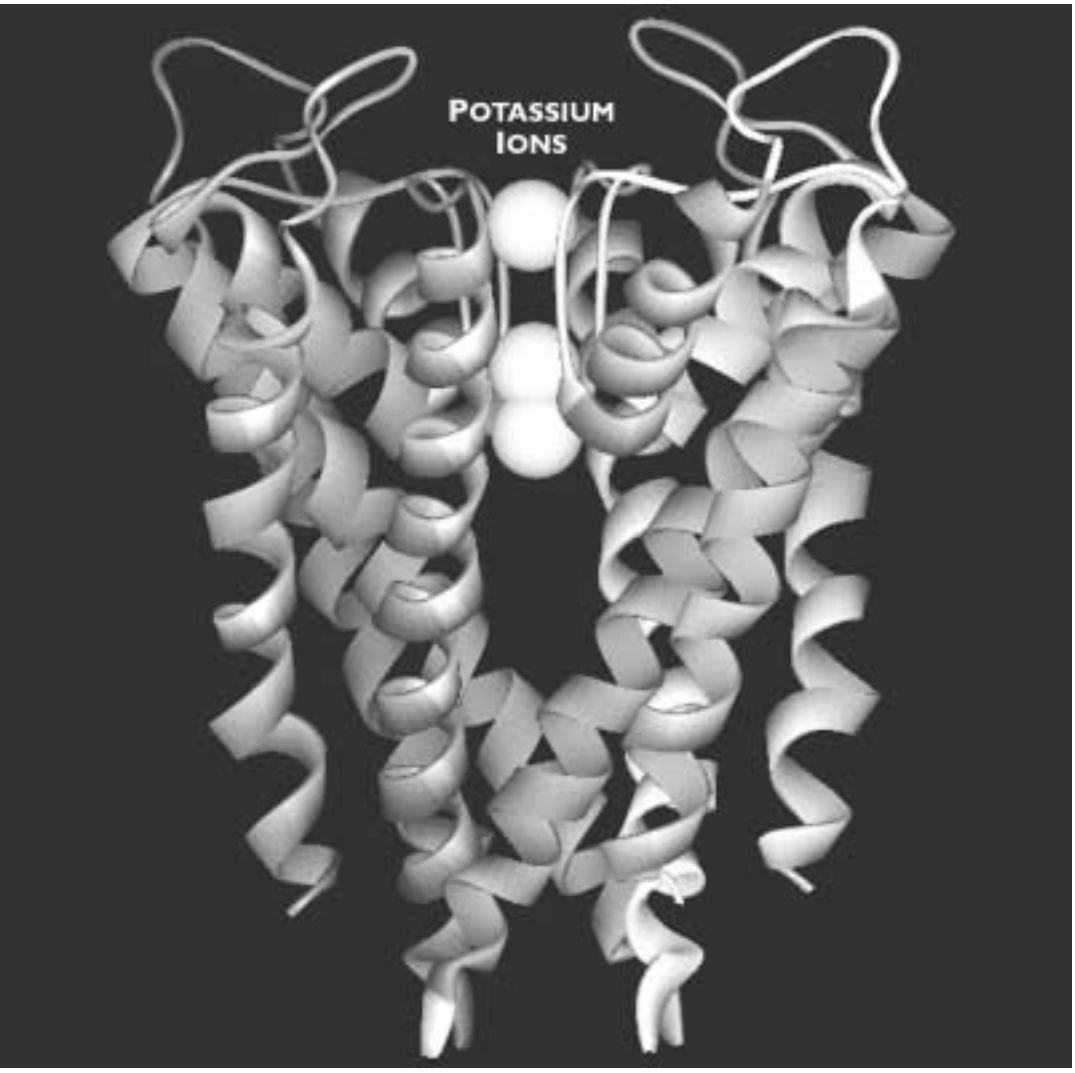
Genetic Medicine

BEGUN JUST OVER A DECADE AGO, the race to completely sequence the human genome is now a sprint to the finish line. With the complete genome sequences of more than a dozen organisms already in hand, and the human genome expected to be completed before 2003, scientists now have access to a virtual treasure trove of information that can be mined for years to come, providing unprecedented insights into the biology of human health and disease. These newly acquired sequencing data also have brought into focus the vast, largely uncharted area now known as proteomics, a field that examines the control mechanisms for gene expression, production of corresponding proteins, and the multitude of interactions between proteins, RNA, and DNA that make an organism a functioning entity.

Dr. John Postlethwaite studies the genome of the zebrafish *Danio rerio* to gain insight into the genes and proteins important to human health. *Photo by Jack Liu, Eugene, Oregon*

To understand how this complex machinery works, researchers have turned to relatively simple creatures such as zebrafish, roundworms, and even single-celled organisms. Comparing the gene structures of these primitive animals with human genes has shown clearly that many genes have been conserved practically unchanged through millions of years. This knowledge, in turn, will form the basis for new initiatives in disease treatment. NCRR is involved in all aspects of these cutting-edge advances by supporting animal resources as well as sophisticated instrumentation and clinical research.

Zebrafish Genes Provide Insights Into Human Genetics and Disease. Scientists are making enormous strides in their efforts to map the genome of the zebrafish *Danio rerio*, a 1-inch-long vertebrate that's increasingly studied as a model for human embryonic development and other gene-related processes. Using complementary approaches to map and sequence the fish's genome, collaborating teams of NCRR-supported investigators have plotted



The three-dimensional structure of a potassium ion channel reveals the narrow passageway through which ions cross the cell membrane.
Image courtesy of Dr. Roderick MacKinnon, Rockefeller University

the positions of several hundred genetic markers, or "milestones," and have found large chromosomal segments, as well as several genes, that closely resemble those of humans.

One newly discovered similarity between human and fish genes has identified the first animal model for an inherited human disorder known as congenital sideroblastic anemia (CSA), which often causes death at a relatively young age. Patients with CSA have too few red blood cells; low levels of the cells' oxygen-carrying component, hemoglobin; and iron overload.

By studying mutant zebrafish that have CSA-like symptoms, a team of NCRR-supported investigators, based in part at Harvard Medical School in Boston, discovered that affected fish have mutations in a gene known as *alas2*, which is also defective in humans with CSA. The gene encodes an enzyme that helps to produce hemoglobin. Further experiments revealed unexpected abnormalities in blood cell formation in the mutant zebrafish embryos, which may help to clarify the mechanisms behind the human disease.

—*Genome Research* 9:334-347, 1999; *Methods in Cell Biology* 60:149-163, 1999; *Nature Genetics* 20: 244-250, 1998.

Structure and Abnormality of the Potassium Channel. Ion channels located in cell membranes create and maintain critical ion concentration differences between the interior and exterior cell surfaces. Ion channel function is essential for operation of the nervous system, muscles, and heart. Although several important drugs that affect ion channels—

such as a heart drug that modifies calcium ion channels—have been developed and are in use, the structural details of these channels were unknown. But now scientists using an NCRR-supported synchrotron light source for X-ray crystallography have determined the three-dimensional detailed structure of a potassium ion channel protein from the fungus *Streptomyces lividans*, which is similar to potassium channels from other organisms, including humans. The structure shows how the channel can selectively allow potassium ions to pass through. Knowing the structure and function of ion channels will help researchers develop better drugs for disorders affecting these channels, including epilepsy.

In a related set of clinical studies, NCRR-supported investigators at the University of Utah in Salt Lake City used a technique known as linkage analysis to pinpoint a gene responsible for an inherited form of epilepsy known as benign familial neonatal convulsions (BFNC). Children with BFNC typically have seizures during the first 4 days of life. Structural studies of the disease-causing gene showed that it encodes a potassium channel protein with a single amino acid mutation. Because the malformed protein cannot properly regulate the flow of potassium ions, the excitability of nerve cells is altered, and seizures result.

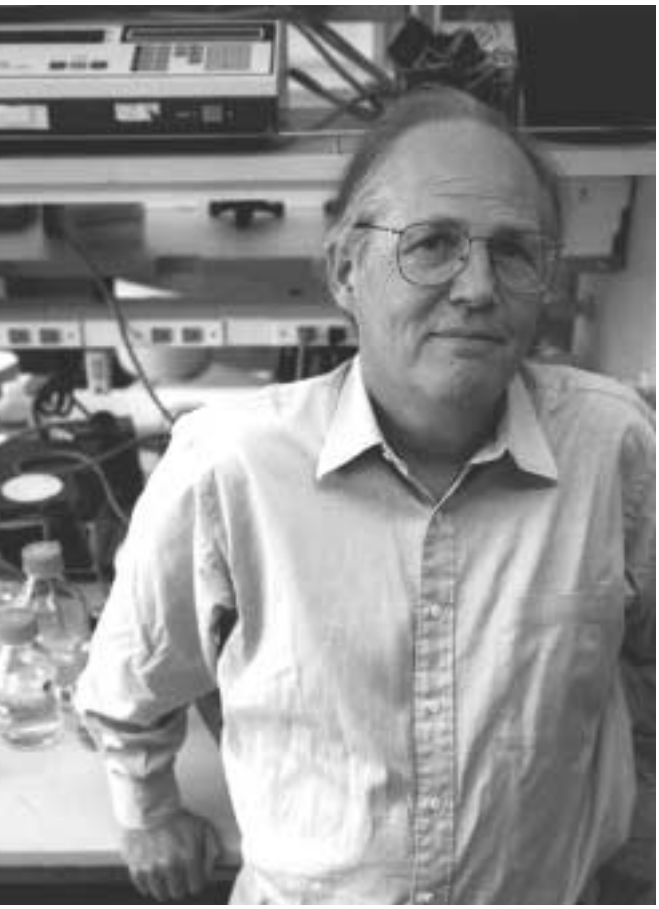
—*Science* 280:69-77, 1998;
Nature Genetics 18:25-29, 1998.

Deaf Mice Lead Researchers to Human Gene. Scientists at the University of Michigan, Ann Arbor, in collaboration with investigators at the National Institute of Deafness and Other Communication Disorders, have isolated a gene that is responsible for an inherited form of deafness in both mice and humans. For some of the most delicate and critical operations in this study, the researchers used equipment purchased in part with an NCRR Shared Instrumentation Grant.

The search for the gene began when investigators noticed similarities between inherited deafness in an Indonesian family and in the *shaker-2* strain of mice. Further investigation revealed that the human deafness gene, known as *DFNB-3*, was located in a region of human chromosome 17 that was analogous to the *shaker-2* gene region on mouse chromosome 11.

To identify the exact chromosomal position of the murine deafness gene, the researchers cut and packaged relevant segments of the normal gene into bacterial artificial chromosomes, injected them into fertilized embryos of deaf mice, and observed any impact on the newborn animals' ability to hear. The procedure successfully prevented hearing loss in one male mouse, while its siblings were insensitive to sound intensities of 90 decibels.

A gene for inherited deafness in mice led Dr. Sally Camper and her colleagues to discover a similar gene for deafness in humans. *Photo courtesy of the University of Michigan*



Dr. Mark Leppert and colleagues at the University of Utah found that defective potassium channels are responsible for an inherited form of epilepsy that causes severe seizures in newborns. *Photo by Ryan Galbraith, Salt Lake Tribune*

After sequencing the chromosomal segment containing the hearing gene, the researchers identified it as belonging to a class of genes that encode proteins known as "unconventional myosins." Two other genes of this type are known to cause hearing loss if defective. The scientists then used the mouse gene as a DNA probe to identify and isolate the homologous human gene.

The functions of the unconventional myosins are not fully understood, but they are known to be required for proper hair cell function in the inner ear. Future studies will show if gene therapy in humans can restore hearing in people who have a defect in that gene.

—*Science* 280:1444-1451, 1998; *Genomics* 55:348-352, 1999.

Gene Contributes to Muscle Loss in HIV. Patients with AIDS and certain types of cancer often experience muscle loss, which causes weakness and reduces quality of life. To better understand the molecular factors that contribute to muscle wasting, NCRR-supported researchers at Charles R. Drew University of Medicine and Science in Los Angeles, California, cloned and examined the human gene for myostatin, a protein known to inhibit growth of skeletal muscle in animals.

By examining myostatin gene expression in biopsied muscle tissue, the investigators found markedly increased expression in specimens from HIV-infected men with weight loss, compared to healthy volunteers. Serum levels of myostatin were also elevated in the HIV-infected patients. The scientists propose that blocking the production or effects of myostatin might offer therapeutic benefits to patients with AIDS-associated wasting or other conditions marked by muscle loss.

—*Proceedings of the National Academy of Sciences USA* 95:14938-14943, 1998.

Sequencing the Worm. A milestone was reached in biological research with the first complete DNA sequencing of a multicelled animal, the tiny soil-dwelling worm *Caenorhabditis elegans*. The worm's genome consists of approximately 19,900 predicted genes distributed on six pairs of chromosomes. A comparison with the thousands of human genes that have been identified shows that about 70 percent are identical or very similar to genes in the worm. NCRR enables study of this valuable animal model

by supporting several *C. elegans*-related research resources, including the world-renowned Caenorhabditis Genetics Center at the University of Minnesota in St. Paul.

In one recent investigation, scientists identified a gene that appears to prolong the worm's life by manufacturing an enzyme that prevents free-radical damage. Free radicals, highly reactive compounds that can ravage DNA, are believed to contribute to the aging process and to several disorders, including Alzheimer's disease. Although a comparable gene has not yet been identified in humans, studies of the worm enzyme (known as cytosolic catalase) are expected to yield basic insights into the mechanisms of free-radical injury and its prevention.

—*Science* 282:2012-2017, 1998; *Nature* 399:162-166, 1999.

The millimeter-long roundworm *Caenorhabditis elegans* was the first multi-celled organism to have its genome completely sequenced.
Photo by Bill Love

New Approaches to Pathogenesis

TO WIN A BATTLE, ONE FIRST MUST KNOW THE ENEMY— whether it be on the playing field, on the battlefield, or within the body in the form of disease-causing genes or microbes. The study of pathogenesis—the process by which a disease originates and develops—has long been dominated by clinical observation, microscopic inspection, and biochemical analyses. But today a plethora of new technologies offer unprecedented opportunities for scrutinizing the genes, proteins, and microorganisms that contribute to disease. These new approaches to pathogenesis offer remarkable insights into the workings of the body and the protection of human health. The studies described below illustrate the breadth of NCRR's support of this cutting-edge science, ranging from advances in infectious disease research to detailed studies of molecular structure, which reveal a vitamin's potential role in disease prevention.

The deadly tropical disease schistosomiasis is caused by the parasite *Schistosoma mansoni*, shown here in the free-swimming cercaria stage, which infects humans. *Scanning electron micrograph by Dr. W. O. Granath, University of Montana*

In Vitro Culture of Parasite Opens Door to Detailed Studies. The *Schistosoma* parasite, which causes the tropical disease schistosomiasis in humans, infects more than 200 million people worldwide and causes extensive morbidity and mortality in developing countries. Because of the parasite's complex life cycle—including temporary residences in both water snails and humans—attempts to grow *Schistosoma* in culture have failed, greatly hindering development of effective drugs and vaccines.

But now researchers at Oregon State University in Corvallis and the NCRR-supported American Type Culture Collection in Manassas, Virginia, have succeeded in developing long-term continuous cultures of *Schistosoma mansoni* in the sporocyst stage of its life cycle, which normally develops in

the snail. The cultured sporocysts, in turn, are capable of developing into the free-swimming cercaria stage, which infects humans. The successful culture conditions were made possible by coculturing the parasite sporocysts with snail embryo cells.

The ability to obtain significant quantities of parasites at particular developmental stages enables study of stage-specific gene activation and identification of enzymes and other factors that are required for the parasite's development and infectivity. These efforts may ultimately lead to rational design of novel therapeutic agents that are more specific and effective than current ones.

—*Proceedings of the National Academy of Sciences USA* 96:4965-4970, 1999.

Human Enzyme Deficiency Model for Gene Therapy. Enzymes known as acyl-CoA dehydrogenases have an essential role in the metabolism of fatty acids. A lack of these enzymes, which are encoded by genes in the cell nucleus but functioning in the cellular power stations called mitochondria, causes recurrent, sometimes life-threatening, disease symptoms. In searching for a potential cure for these diseases, which are caused by mutations in the enzyme-encoding genes, NCRR-supported researchers at the University of Alabama at Birmingham have identified and studied mice that have genetic acyl-CoA dehydrogenase diseases very similar to the human diseases. In recent studies the scientists injected DNA containing a missing acyl-CoA dehydrogenase gene into fertilized eggs of the mouse disease model. The mice that subsequently were born with the active gene had normal enzyme activity and appeared cured of their defect.

In other studies, the investigators cloned and characterized the entire mouse gene encoding long-chain acyl-CoA dehydrogenase. The gene is present as a single copy containing 11 coding regions (exons) and consisting of approximately 35,000 base pairs. These studies show the crucial roles of these mitochondrial enzymes and provide important basic and practical therapeutic information for potential gene therapy of the corresponding human diseases.

—*Mammalian Genome* 9:361-365, 1998; *Proceedings of the National Academy of Sciences USA* 95: 15592-15597, 1998.

Ferreting Out the Functions of Folate. Because the B vitamin folic acid has been shown to reduce blood levels of homocysteine, a compound associated with cardiovascular disease and severe birth defects, many foods are now enriched with folic acid and prospective mothers are urged to take the vitamin both before and during pregnancy. But despite dozens of clinical and animals studies, the molecular mechanism by which folic acid quashes homocysteine levels has remained unclear.

Structural biologists are now providing a critical piece of the puzzle. Using crystallography equipment purchased with an NCRR Shared Instrumentation Grant, and working at an NCRR-supported synchrotron facility, researchers at the University of Michigan in Ann Arbor have discovered the detailed structure of an enzyme known as methylenetetrahydrofolate reductase (MTHFR), which helps to convert homocysteine to methionine, a beneficial amino acid. The structural studies revealed that MTHFR functions properly only when clutching a small flavin molecule derived from folic acid. If the MTHFR enzyme is abnormal, as it is believed to be in about

10 percent of the human population, then it readily loses its grip on the flavin molecule and becomes deactivated, thereby preventing the conversion of homocysteine. The researchers also found evidence that high levels of folate may help to tighten the bond between flavin and MTHFR—a clue to how folic acid supplements can reduce homocysteine levels in patients with normal or mutant forms of MTHFR.

Meanwhile, a series of NCRR-supported investigations at the Oregon Health Sciences University in Portland are helping to demonstrate folic acid's benefits and homocysteine's harm to the human body. One study reported that breakfast cereals fortified with folic acid can significantly reduce homocysteine levels in patients with heart disease, and the other—an ongoing study of more than 350 patients reporting third-year results—revealed that elevated homocysteine levels are associated with death from cardiovascular disease and worsening of atherosclerosis in patients with arterial disease.

—*Nature Structural Biology* 6:359-365, 1999; *New England Journal of Medicine* 338:1009- 1014, 1998; *Journal of Vascular Surgery* 29:8-21, 1999.

Receptor-Specific Chimeric Viruses Model HIV-1 Infection. Chimeric AIDS viruses, called SHIVs (simian-human immunodeficiency viruses), in which scientists have replaced the SIV (simian immunodeficiency virus) envelope proteins with HIV-1 envelope proteins, infect macaque monkeys and mimic many of the events associated with HIV-1 infections of humans. To study the influence of different lymphocyte receptors on the infection process, scientists produced SHIVs that are specific for two different receptors and found that each is associated with a distinct infection process.

Investigators at the Aaron Diamond AIDS Research Center in New York City collaborated with researchers at the NCRR-supported Tulane Regional Primate Research Center in Covington, Louisiana, to produce the receptor-specific viruses. One type of SHIV infects lymphocytes through a receptor known as CCR5 (R5), while another gains entry to cells by attaching to a receptor known as CXCR4 (X4). In the early phase of infection of macaque monkeys, the R5-specific virus caused a dramatic loss of $CD4^+$ intestinal T cells but only a transient loss of peripheral $CD4^+$ T cells. In contrast, the X4-specific SHIV caused a profound loss of peripheral T cells that was not accompanied by loss of intestinal T cells. The differing routes of infection lead to distinctive modes of pathogenesis, which contribute to the complexities of combatting the AIDS virus.

By uncovering a detailed three-dimensional structure of an enzyme known as MTHFR, Drs. Rowena Matthews (left) and Martha Ludwig discovered how the enzyme's shape is crucial to converting homocysteine to methionine, a beneficial amino acid. *Photo courtesy of the University of Michigan*

These results support the use of SHIV infection of macaques as a reliable in vivo model for preclinical examination of potential HIV-1 vaccines and therapeutic agents in the context of HIV-1 envelope proteins.

—*Science* 284:816-819, 1999.


DUKE
Radiology

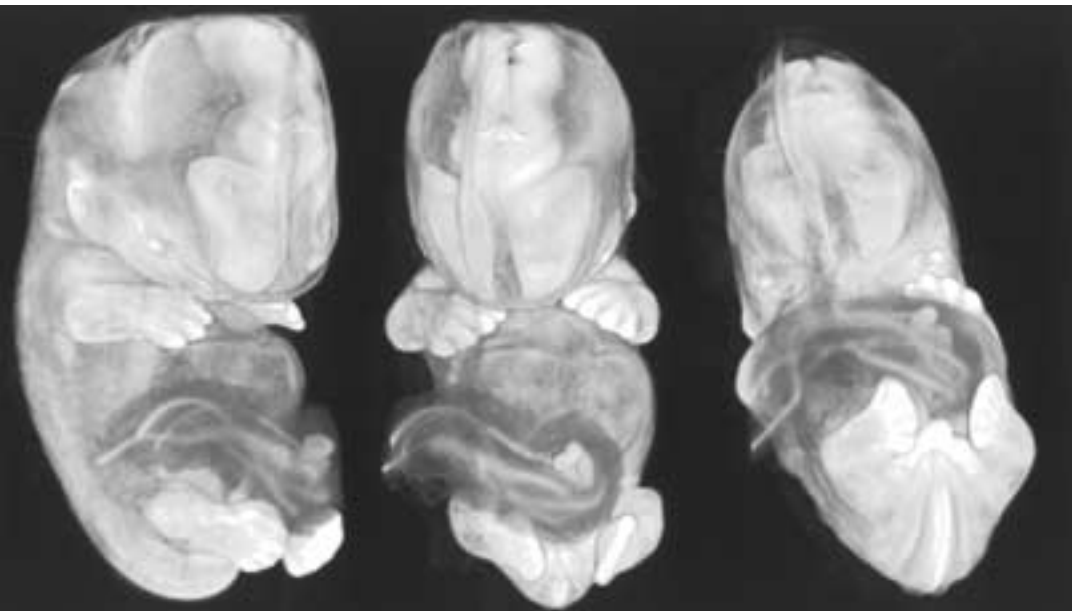
Bioengineering, Computers, and Advanced Instrumentation

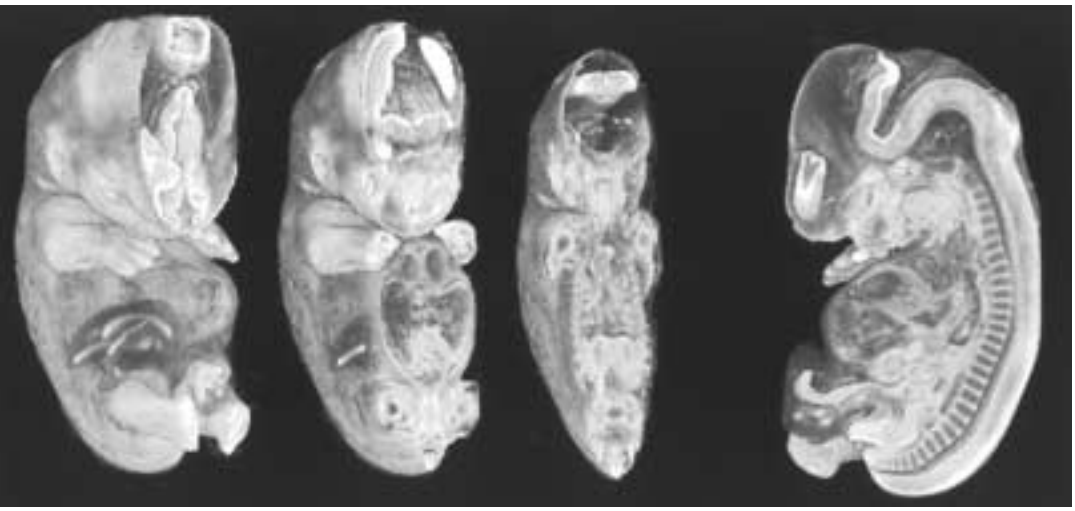
A COMPLETE UNDERSTANDING OF THE HUMAN BODY in health and disease requires the capacity to visualize and study its parts in situ. The recent, almost explosive developments in computer technology, imaging, and microengineering have made it possible to accomplish this feat.

Dr. Bradley Smith and his colleagues use custom-built tools and instruments to image small animals and developing embryos in three dimensions. *Photo by Elaine Fitzsimons, Duke University Medical Center*

Noninvasive imaging technologies and advanced instrumentation are opening new horizons in areas ranging from embryology to ophthalmology to breast cancer screening, and tiny electrodes eavesdrop on the traffic patterns among individual neurons in the brain. By supporting biomedical technology resource centers, synchrotron facilities, supercomputers, and acquisition of cutting-edge equipment through Shared Instrumentation Grants, NCRR is an essential participant in this technological revolution.

Three-Dimensional Imaging on a Smaller Scale. Magnetic resonance imaging (MRI) is a widely used technique that helps clinicians locate internal tumors and image organs noninvasively. But until recently the full potential of MRI has not been utilized because of technical difficulties in scaling down the procedure. For example, researchers studying human development or small animal models of human diseases would benefit from being able to monitor organ development or characterize the internal topography of mutant mice and other small animals. Now investigators at the NCRR-supported Center for In Vivo Microscopy at Duke University in Durham, North Carolina, have succeeded in bridging this size gap. Thanks to carefully crafted computer algorithms and other computational techniques developed by the Duke scientists, imaging data obtained via





In these three magnetic resonance microscopy (MRM) images (top) of a 33- to 34-day-old human embryo—the size of a kidney bean—the left and right hemispheres of the forebrain and midbrain are visible, and the digits of hands and feet are beginning to take form.

The "sliced" MRM images (bottom) reveal interior details of the brain, heart, and spinal cord. *Images courtesy of the Center for In Vivo Microscopy, Duke University*

miniaturized MRI—known as magnetic resonance microscopy, or MRM—are merged to create a three-dimensional (3-D) isotropic reconstruction of the specimen, which means that the image can be viewed equally well from any angle.

MRM has been used in the Multidimensional Human Embryo project to create detailed interior and exterior 3-D images of 18 whole human embryos obtained from another NCRR-supported resource, the Human Developmental Anatomy Center, which is part of the National Museum of Health and Medicine at the Armed Forces Institute of Pathology in Washington, DC. The images, representing human developmental stages that occur during the first two months after conception, are available to the scientific community via the Internet and may be used for teaching purposes.

In studies on small animals such as rats, the anatomical locations of brain lesions are conventionally identified on histological sections. In contrast, using MRM, the Duke researchers can rapidly identify and visualize lesions in three dimensions in fixed intact rat brains. These studies show that MRM has the potential to become a widely applicable examination tool in anatomical/pathological studies of small specimens.

—*Computerized Medical Imaging and Graphics* 23:33-40, 1999; *Neuroreport* 10:737-741, 1999.

Teleophthalmology Delivers Eye Care to Underserved Populations. Diabetic eye disease—the leading cause of blindness and visual

impairment in American adults—often hits minority populations hardest. Previous studies suggest that African Americans and Hispanics with diabetes have more severe retinopathy than white diabetics of similar age and gender. But with early diagnosis and access to adequate health care, many of the problems associated with diabetic eye disease can be prevented or treated.

With support from NCRR's Research Infrastructure area, investigators at the Charles R. Drew University of Medicine and Science in Los Angeles, California, are using state-of-the-art computing and communications technologies to deliver medical expertise and health care to underserved populations in South Central Los Angeles, where many of the 1.4 million residents live at or below the poverty line.

In a pilot project launched in late 1996, the researchers began to offer free "teleophthalmology" eye examinations to residents of a local housing project. Preliminary eye assessments are conducted at an on-site clinic, eliminating the need for patients to travel, and clinical data and ocular images are telecommunicated to physicians at Drew University, who evaluate each patient's eye condition and prescribe treatments or suggestions for follow-up care. These long-distance examinations have provided accurate diagnoses in 90 to 95 percent of cases, and about 90 percent of patients have followed up on medical instructions.

Dr. Charles Flowers evaluates an eye scan of a patient who is at a distant site. Telemedicine promises to improve access to health care and medical specialists in underserved populations.
Photo by Lawrence Givens, Charles R. Drew University of Medicine and Science

The researchers have now widened their geographic reach by opening new telemedicine clinics in additional public housing communities. The program not only benefits the local residents, who now have improved access to medical specialists, but it also provides a uniquely detailed data set by which researchers can evaluate health issues that concern minority populations.

—*Ophthalmology* 105:1373-1378, 1998.

"Virtual Cell" Melds Data From Many Disciplines. Thanks to recent technological advances, biologists now have the ability to study cell structure and function in unprecedented detail. But the wealth of information offered by genetic, molecular, biochemical, and structural studies can at times seem unmanageable and unconnected, with important relationships concealed within unwieldy datasets, awaiting discovery.

A new computational tool known as the Virtual Cell, now under development at the NCRR-supported National Resource for Cell Analysis and Modeling, may help scientists to map the wilderness. In many ways the Virtual Cell is a virtual melting pot, culling and integrating disparate data about cellular structure (acquired via microscopy) and cellular function (acquired via biochemical and electrophysiological experiments). By merging and graphically displaying a variety of experimental findings, the Virtual Cell offers new insights into cell biology and drug development.

In their start-up efforts, scientists at the resource—located at the University of Connecticut Health Center in Farmington—are laying the groundwork for more complex models by first simulating well-defined processes, such as RNA trafficking and calcium signaling in neurons and cardiac muscle cells. The Virtual Cell will ultimately enhance understanding of how the dimensions of a cell and its organelles help to orchestrate the molecular events that influence a cell's behavior.

Drs. Leslie Loew and Ann Cowan, together with an interdisciplinary team of scientists, have designed a computer modeling tool known as the Virtual Cell, which creates simulations of cellular behavior. *Photo courtesy of University of Connecticut Health Center*

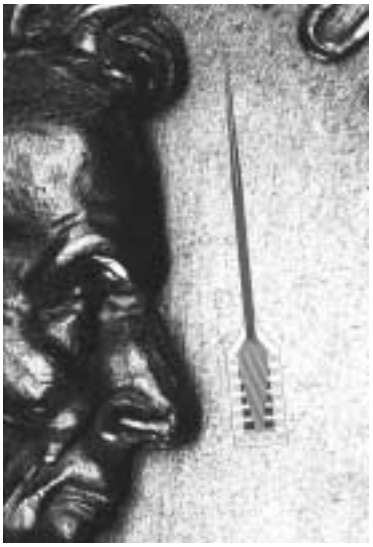
—*Proceedings of the National Academy of Sciences USA* 96:6700-6704, 1999.

Pinpointing the Location of Sounds. Most animals and humans can identify the location of sounds that have a broad spectrum of frequencies, such as a singing bird, a honking horn, or rustling leaves. But when the sound has a narrow band of frequencies, such as a beeping pager, localization becomes much more difficult. To better understand this phenomenon, researchers studied how the brain responds to various sounds by inserting neural probes the size of a grain of pepper into the auditory cortex of cats. The probes, created at the Michigan Center for Neural Communication in Ann Arbor, were able to

record the firing of single neurons in response to sounds of broad or narrow bandwidth. Each type of sound produced a characteristic firing pattern of the neurons, which helps the animal to locate the origin of the sound.

Although the cats located broad-band sounds correctly, they consistently misjudged the location of narrow-band sounds and made predictable perceptual errors comparable to those seen in human experiments in which people turned toward a sound's perceived origin. If future studies confirm that neurons in the human auditory cortex respond similarly to cat neurons, they will have immediate application in the development of implantable hearing devices designed to stimulate the auditory system directly.

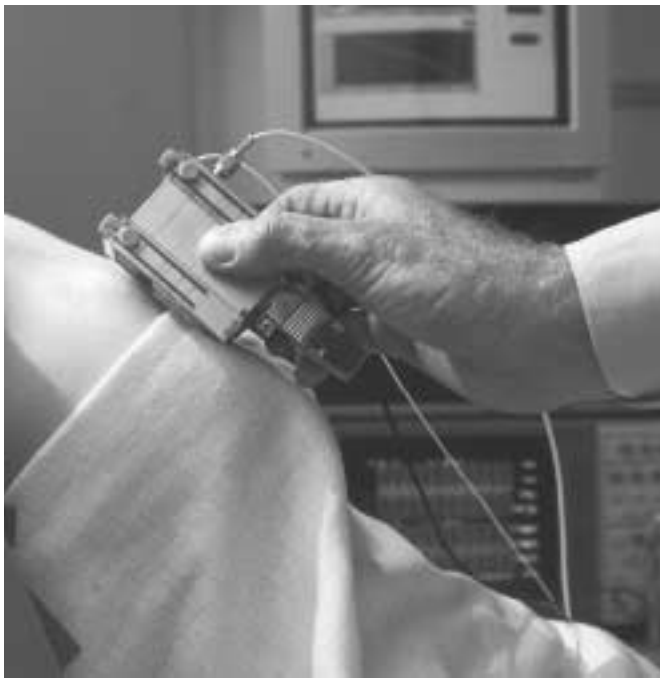
—*Nature* 399:688-691, 1999.



This 16-channel recording probe, created at the NCRR-supported Michigan Center for Neural Communication Technology, is smaller than Lincoln's head on a penny. *Photo by Jamie Hetke, University of Michigan*

Bright Future for Optical Mammography. Conventional mammography, which uses X-rays to scan for tumors, is a mainstay of breast cancer screening. Nevertheless, X-ray mammography has a number of drawbacks, including failure to detect half of all cancerous tumors in women between the ages of 40 and 50 and the inability to distinguish between malignant and benign tumors. To overcome these problems, several NCRR-supported biomedical technology resource centers have developed optical scanners that use infrared light instead of X-rays. The presence of a tumor distorts light in a characteristic way, and in contrast to X-rays, optical imaging methods can provide functional information about the breast tissue. For example, hemoglobin absorbs infrared light at two different wavelengths, depending on whether the molecule is in its oxygen-carrying or deoxygenated form. Because a tumor is characterized by an increase in the number of blood vessels, it has a higher content of hemoglobin than surrounding healthy tissue and can therefore be identified. This new technology is being tested in clinical trials in the United States and Europe.

—*Photochemistry and Photobiology* 67:15-22, 1998.



University of California scientists have developed a hand-held optical device that noninvasively detects and analyzes suspicious breast lesions. Now being tested in clinical trials, this new technology may provide a more specific diagnosis than X-ray mammography and thereby prevent unneeded surgery. *Photo by Paul Kennedy*

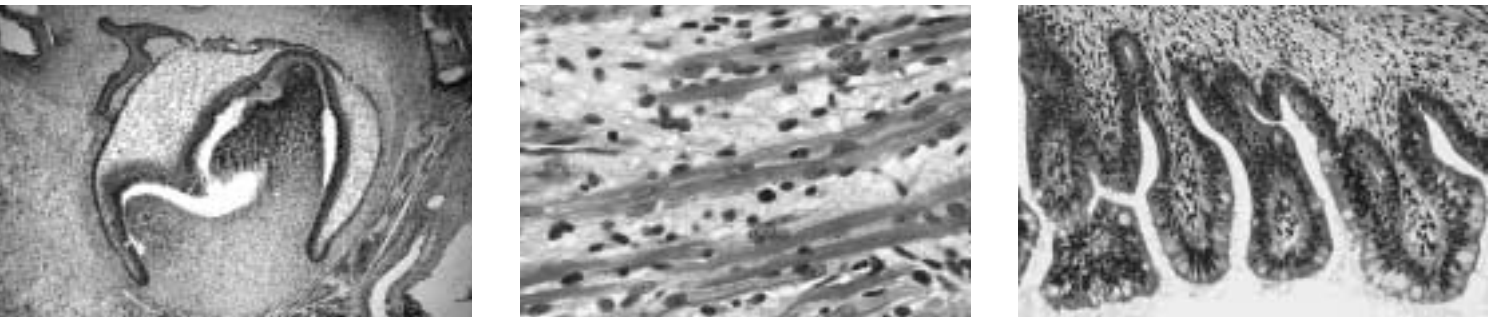
New Avenues for Development of Therapeutics

THE DEVELOPMENT OF NEW THERAPEUTIC APPROACHES to treat diseases requires participation by investigators working in such disparate areas as virology, embryology, molecular modeling and imaging, and bioinformatics. The long discovery process includes basic in vitro and animal studies and ends with careful clinical evaluations that record therapeutic benefits and any adverse reactions. By providing the tools, animals, and infrastructure that are essential for cutting-edge research, NCRR contributes to all aspects of this multidisciplinary development of new therapies.

Dr. John Freeman assesses the progress of a young epilepsy patient by asking him to balance a coin on his nose. *Photo by Keith Weller, Johns Hopkins Children's Center*

The Embryonic Stem Cell, Mother of All Cells. Embryonic stem (ES) cells are undifferentiated cells that have the potential to mature into any type of tissue cell. In a ground-breaking 1995 study, NCRR-supported researchers at the Wisconsin Regional Primate Research Center in Madison isolated and cultured ES cells from macaque monkeys. Drawing on this experience, in 1998 the investigators were among the first to report the isolation and culturing of comparable human cells, which have the potential to differentiate into any type of body tissue. Properly maintained and cultivated, human ES cells may one day be used to produce donor tissues for transplantation or serve as a basis for other novel therapeutics.

But before ES-based remedies can reach the clinic, they must be thoroughly evaluated in animal models to demonstrate safety and efficacy. The Wisconsin investigators are therefore continuing to study ES cells from nonhuman primates and have established several collaborations to examine ES-derived neural and blood cells. Transplantation of



NCRR-supported scientists showed that monkey embryonic stem (ES) cells could differentiate into tooth-, muscle-, and gut-like tissues (shown above, from left to right). These pioneering investigations laid the groundwork for the culturing of human ES cells, which hold promise for treating a variety of human diseases. *Photos by James Thomson, Wisconsin Regional Primate Research Center*

these specific derivatives may be evaluated as potential therapies for Parkinson's disease and leukemia in animal models.

—*APMIS* 106:149-156, 1998; *Science* 282:1145-1147, 1998.

Ketogenic Diet for Childhood Epilepsy. Most cases of epilepsy in children are easily brought under control with medication, but a few are unresponsive to conventional drugs. These children may benefit from treatment with a special high-fat, low-protein diet known as the ketogenic diet because it boosts the body's production of ketones, the metabolic "ash" or byproducts of incompletely burned fats. High levels of ketones in the blood have been found to reduce the frequency of seizures dramatically.

Researchers at the NCRR-supported pediatric General Clinical Research Center at Johns Hopkins University Hospital in Baltimore, Maryland, studied 150 children, 1 to 16 years old, over a two-year period. These children had a minimum of two seizures a week—and averaged 410 seizures per month—despite treatment with at least two anti-convulsant drugs. Most of the children were started on a diet that contained fat to protein plus carbohydrate in a four-to-one ratio. The diet was subsequently adjusted to obtain optimal tolerance and seizure control.

Three months after starting on the diet, 83 percent of the children remained on the diet, and 34 percent had a greater than 90 percent decrease in seizures. After one year, 55 percent of the children were still adhering to the diet, and 27 percent had a greater than 90 percent reduction in seizures. The researchers recommend that the ketogenic diet should be considered as an alternative therapy for children with difficult-to-control seizures. They emphasize that the diet should be used only under medical and nutritional supervision.

—*Pediatrics* 102:1358-1363, 1998.

Prompting Cancer Cell Suicide. Recently acquired molecular details of the cell cycle allow scientists to explore novel routes for selectively destroying cancer cells. In one pioneering effort, researchers at the Dana-Farber Cancer Institute in Boston,

Massachusetts, are targeting a precise molecular pathway that involves the retinoblastoma tumor suppressor protein (pRB), which is a critical contributor to the normal cell cycle but is deactivated in tumor cells.

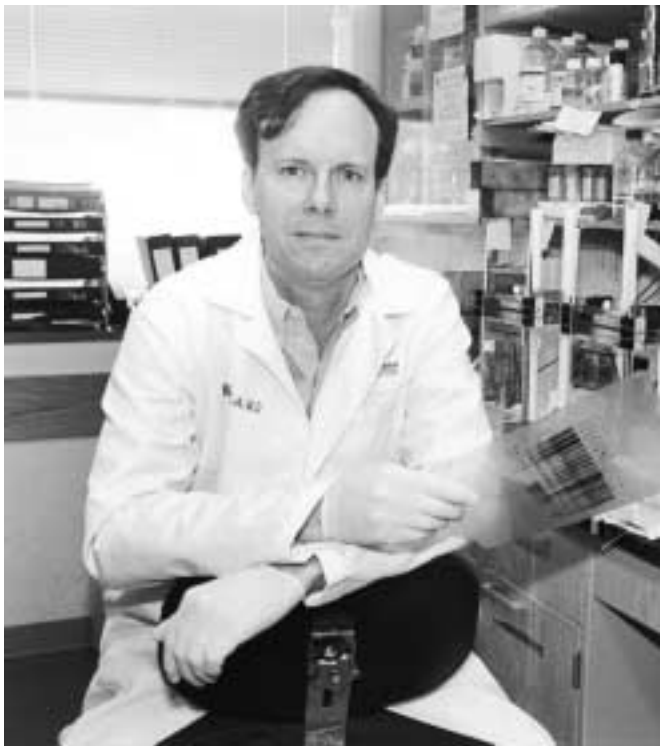
Using state-of-the-art flow cytometry equipment purchased via an NCRR Shared Instrumentation Grant, the scientists developed and tested small peptides that were shown to enter cells and prevent binding of two cell-regulating complexes whose levels are altered by pRB deactivation. By blocking this molecular interaction, the peptides ultimately triggered self-destruction of tumor cells but left normal cells unharmed. The scientists suggest that similar cell-cycle-blocking compounds may prove useful as cancer-fighting drugs.

—*Proceedings of the National Academy of Sciences USA* 96:4325-29, 1999.

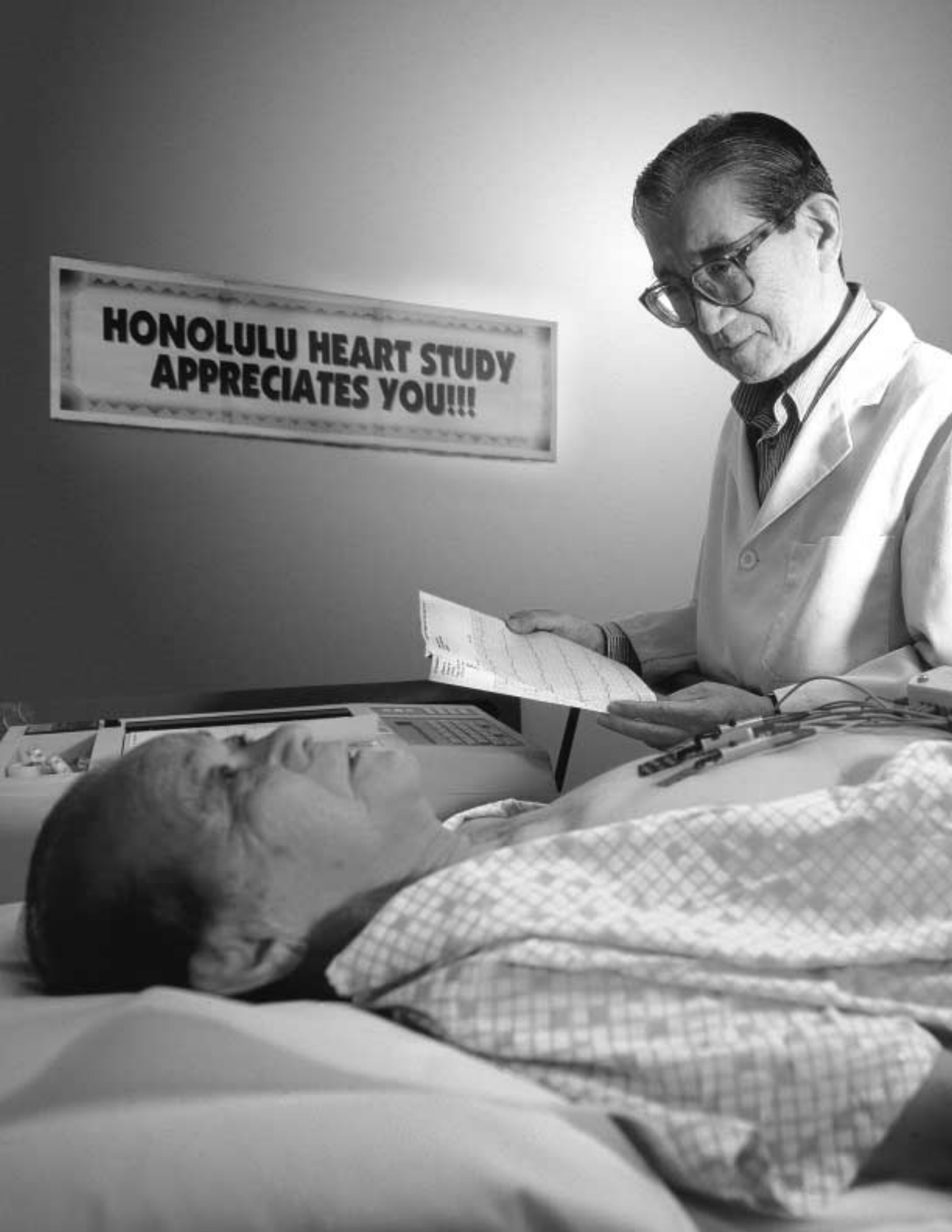
Studying the Mechanism of Cell Transformation. When a normal cell undergoes changes that transform it into a tumor cell, both its outward appearance and internal chemistry change. Investigators at Hunter College of the City University of New York, partly supported by an NCRR Research Centers in Minority Institutions grant, are studying biochemical events involved in cell transformation caused by a group of cancer-causing genes known as oncogenes.

Cells that previously have been growing in one-cell-thick sheets may suddenly begin to "crawl" and form clumps on top of one another or even disassociate completely and form new colonies. In the body such cell transformations give rise to tumor growth and metastases. Inside transformed cells, previously dormant genes may become active and produce enzymes and other cell components that are characteristic of particular tumor cell types. These studies have revealed novel potential targets for therapeutic intervention in the treatment of cancer.

—*Biochemical and Biophysical Research Communications* 255: 502-507, 1999.



Dr. William Kaelin, Jr., and his colleagues have synthesized a peptide that forces cancer cells to commit suicide. *Photo courtesy of Dana-Farber Cancer Institute*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New Preventive Strategies Against Disease

THE WORLDWIDE PREVENTION AND ERADICATION of smallpox and the prevention of polio in western Europe and North America by mass immunizations are among the most striking examples of the benefits of disease prevention. Currently, numerous laboratories are working on development of vaccines to prevent AIDS, malaria, and other global diseases.

Dr. Katsuhiko Yano checks an electrocardiogram of a volunteer participating in a clinical study of heart health in Hawaii. *Photo courtesy of University of Hawaii*

But not all diseases can be prevented by immunizations. An increasing number of studies suggest that a sensible lifestyle that provides a clean environment, moderate amounts of food and vitamins, uncontaminated drinking water, and physical activity has an enormous impact on general health. For example, eating too much causes obesity, heart disease, and diabetes; physical inactivity weakens muscles, resulting in falls; and vitamin deficiency may cause stroke. Through its support of both animal and clinical preventive studies, NCRR is involved in creating a healthier society.

Walk for Your Life! Although it is well recognized that exercise is beneficial, the cardiovascular and life-lengthening effects of low-intensity activities such as walking have not been clearly documented. Now multidisciplinary groups of investigators—partly supported by NCRR's Research Centers in Minority Institutions (RCMI) Program—report that older, physically capable men who walk regularly have a considerably lower mortality than sedentary men.

The researchers evaluated 707 retired, nonsmoking men who were enrolled in the Honolulu Heart Program, a project that began in 1965 to track the health of more than 8,000 men of Japanese ancestry. At baseline examinations, conducted between 1980 and 1982 when the men were 61 to 81 years old, the men indicated how far they walked each

Dr. Meryl LeBoff found evidence that vitamin D intake may help prevent hip fracture in post-menopausal women. *Photo by John Nordell, Weston, MA*

day. During a 12-year followup period, 43 percent of the men who walked less than one mile per day died, compared to 22 percent of those who walked more than two miles per day. Approximately 6.5 percent of the men who walked the least died of coronary heart disease or stroke, compared to only 2 percent of those who walked the most. Even cancer-related mortality was affected: more than 13 percent of men who walked less than a mile a day died of cancer, compared with only 5 percent of the two-mile walkers. The researchers recommend that older people be encouraged to walk to maintain their health.

—*New England Journal of Medicine* 338:94-99, 1998.

Vitamin D Deficiency in Post-menopausal Women. The risk of hip fractures increases exponentially with age, but some of these injuries may be prevented with adequate vitamin D intake, a new study suggests. Researchers at the NCRR-supported General Clinical Research Center at the Brigham and Women's Hospital in Boston studied 98 post-menopausal women admitted to the hospital for hip replacement; 30 of them, who had acute hip fractures, showed signs of vitamin D deficiency.

Compared to the 68 patients in the control group, who were admitted to the hospital for elective joint replacement, the women with hip fractures had lower levels of the vitamin D precursor 25-hydroxyvitamin D; half of the women with fractures also had insufficient blood levels of vitamin D itself. In addition, levels of parathyroid hormone and other indicators of bone resorption were higher in the women with hip fractures than in those admitted for elective joint replacement.

Although the importance of calcium intake to healthy bones is widely recognized, the researchers say this study should heighten awareness of the concomitant need for adequate vitamin D intake, which is required for efficient calcium absorption and bone mineralization.

—*Journal of the American Medical Association* 281:1505-1511, 1999.

Effect of Diet on Cholesterol. In the multicenter Delta Study, conducted in part by NCRR-supported researchers at Columbia University in New York City and the University of Minnesota in Minneapolis, investigators fed standardized diets to 103 healthy adult men and women, 22 to 67 years old, and subsequently measured cholesterol-related parameters in the blood. In contrast to most previous studies, the Delta Study included both premenopausal and postmenopausal women and African Americans. In a randomized, cross-over study design, the participants received three different diets containing identical numbers of calories but decreasing amounts of saturated fat. The results showed that the stepwise reductions in dietary saturated fat caused corresponding reductions in plasma cholesterol and LDL cholesterol, the so-called "bad" cholesterol. The results were similar in all participants, irrespective of age, race, or gender.

—*Arteriosclerosis, Thrombosis, and Vascular Biology* 18:441-449, 1998.

Blood Transfusion Prevents Stroke in Children With Sickle Cell Anemia. Although blood transfusions are known to prevent recurrent strokes in children with sickle cell anemia, it was unclear if transfusions also could prevent a first stroke. This has now been established so convincingly that investigators terminated the clinical trial early to protect all participating children from this devastating complication of sickle cell anemia.

A total of 130 children with a mean age of 8 years were enrolled in the multicenter trial, partly supported by NCRR's Clinical Research area. The children were selected based on ultrasonic Doppler scans of their brains, which recorded the velocity of the blood flow in their internal carotid or middle cerebral artery. A flow of 200 cm per second or higher—corresponding to partial blockage of the arteries—indicated that the children were at risk for stroke. Of these children, 63 were randomly assigned to receive blood transfusions approximately every 25 days, and 67 to receive standard care.

Only one patient in the transfusion group had a stroke that occurred after 26 months of treatment, but 11 patients in the standard care group had strokes. As a result, the trial was stopped 16 months before the planned termination date. Although these results are promising, the researchers suggest that physicians carefully consider the risks associated with multiple transfusions before deciding to use this treatment.

—*New England Journal of Medicine* 339:5-11, 1998.

Budget Tables

NCRR Funding, Fiscal Year 1998

RESEARCH AREAS	FUNDING	MAJOR SUPPORT
Clinical Research	$170,312,000	■ 75 General Clinical Research Centers ■ 110 Clinical Associate Physician awards ■ 20 Minority Clinical Associate Physician awards ■ 9 Clinical Research Scholar awards ■ 3 National Gene Vectors Laboratories ■ 1 National Disease Research Interchange ■ 1 Conference ■ 3 Research Contracts
Biomedical Technology	$ 93,314,000	■ 64 Biomedical Technology Resource Centers ■ 37 Research Projects ■ 27 Exploratory/Developmental Research Projects ■ 5 Conferences ■ 92 Shared Instrumentation Grants ■ 9 James A. Shannon Director's Awards ■ 2 Research Contracts
Comparative Medicine	$ 95,624,000	■ 7 Regional Primate Research Centers ■ 19 Animal Models/Animal and Biological Materials Resources ■ 5 Program Projects ■ 64 Research Projects ■ 17 Resource-Related Research Projects ■ 5 FIRST Awards ■ 4 Conferences ■ 18 Special Emphasis Research Career Awards (Laboratory Animal Sciences) ■ 14 Institutional National Research Service Awards (NRSA) ■ 4 NRSA-Short-Term Research Training ■ 1 NRSA Individual Postdoctoral Fellowship ■ 10 Cooperative Agreements ■ 2 Research Contracts
Research Infrastructure	$ 67,581,000	■ 18 Research Centers in Minority Institutions (RCMI) ■ 6 RCMI-Clinical Research Infrastructure Initiative ■ Minority Centers for Dental Research (cofunded 2 grants) ■ 7 Research Infrastructure in Minority Institutions (funded by the NIH Office of Research on Minority Health) ■ 9 Institutional Development Awards (IDeA) ■ 7 Shared Instrumentation Grants* ■ 17 Research Projects* ■ 20 Science Education Partnership Awards ■ 75 Competitive K-12 Program Awards ■ K-12 Science Education: Supported 1020 students, 233 inservice and preservice teachers ■ 24 Research Facilities Construction Awards ■ 13 Animal Facilities Improvement Awards ■ 1 Research Contract
Small Business Innovative Research and Small Business Technology Transfer	$ 10,428,000	■ 57 Small Business Innovation Research Awards ■ 6 Small Business Technology Transfer Awards ■ 2 Small Business Innovation Research Contracts
Total Extramural	**$ 437,259,000****	

** Awarded to institutions in IDeA-eligible states.*
*** In addition, $8,628,000 of reimbursable authority from other Federal agencies was obligated by NCRR in FY 1998.*

NCRR Funding, Fiscal Year 1999

RESEARCH AREAS	FUNDING	MAJOR SUPPORT
Clinical Research	$203,906,000	■ 77 General Clinical Research Centers ■ 106 Clinical Associate Physician awards ■ 9 Minority Clinical Associate Physician awards ■ 2 Clinical Research Scholar awards ■ 3 National Gene Vectors Laboratories ■ 1 National Disease Research Interchange ■ 2 Conferences ■ 1 Research Contract ■ 1 Program Project
Biomedical Technology	$ 130,142,000	■ 66 Biomedical Technology Resource Centers ■ 45 Research Projects ■ 27 Exploratory/Developmental Research Projects ■ 139 Shared Instrumentation Grants ■ 4 Research Contracts
Comparative Medicine	$ 112,902,000	■ 8 Regional Primate Research Centers ■ 22 Animal Models/Animal and Biological Materials Resources ■ 1 Program Project ■ 71 Research Projects ■ 24 Resource-Related Research Projects ■ 5 Exploratory/Developmental Research Projects ■ 2 FIRST Awards ■ 4 Conferences ■ 20 Special Emphasis Research Career Awards (Laboratory Animal Sciences) ■ 16 Institutional National Research Service Awards (NRSA) ■ 4 NRSA-Short-Term Research Training ■ 1 NRSA Individual Postdoctoral Fellowship ■ 13 Cooperative Agreements ■ 4 Research Contracts
Research Infrastructure	$ 86,822,000	■ 18 Research Centers in Minority Institutions (RCMI) ■ 6 RCMI-Clinical Research Infrastructure Initiative ■ 3 Centers of Clinical Research Excellence at RCMI eligible institutions ■ Specialized Neuroscience Research Centers (cofunded 5 grants) ■ Minority Centers for Dental Research (cofunded 2 grants) ■ 7 Research Infrastructure in Minority Institutions (funded by the NIH Office of Research on Minority Health) ■ 7 Shared Instrumentation Grants* ■ 75 Research Projects* ■ 2 Specialized-Comprehensive Centers* ■ 23 Science Education Partnership Awards ■ 40 Competitive K-12 Program Awards ■ K-12 Science Education: Supported 1020 students, 233 inservice and preservice teachers ■ 30 Research Facilities Construction Awards ■ 17 Animal Facilities Improvement Awards ■ 1 Research Contract
Small Business Innovative Research and Small Business Technology Transfer	$ 12,479,000	■ 57 Small Business Innovation Research Awards ■ 6 Small Business Technology Transfer Awards ■ 2 Small Business Innovation Research Contracts
Total Extramural	**$ 546,251,000****	

* *Awarded to institutions in IDeA-eligible states.*
** *In addition, $1,264,000 of reimbursable authority from other Federal agencies was obligated by NCRR in FY 1999.*

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_____ *Comparative Medicine Resources Directory (1999)*

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_____ *Fact Sheet: Clinical Research (1999)*

_____ *Fact Sheet: Comparative Medicine (1999)*

_____ *Fact Sheets: Regional Primate Research Centers*

QTY:

_____ *Guide for the Care and Use of Laboratory Animals*

_____ *Integrated Genomics Workshop Report (1999)*

_____ *NCRR: A Catalyst for Discovery brochure*

_____ *NCRR Highlights, 1998-1999*

_____ *NCRR Reporter* magazine (quarterly)

_____ *Plan for the National Center for Research Resources: 1998-2003*

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